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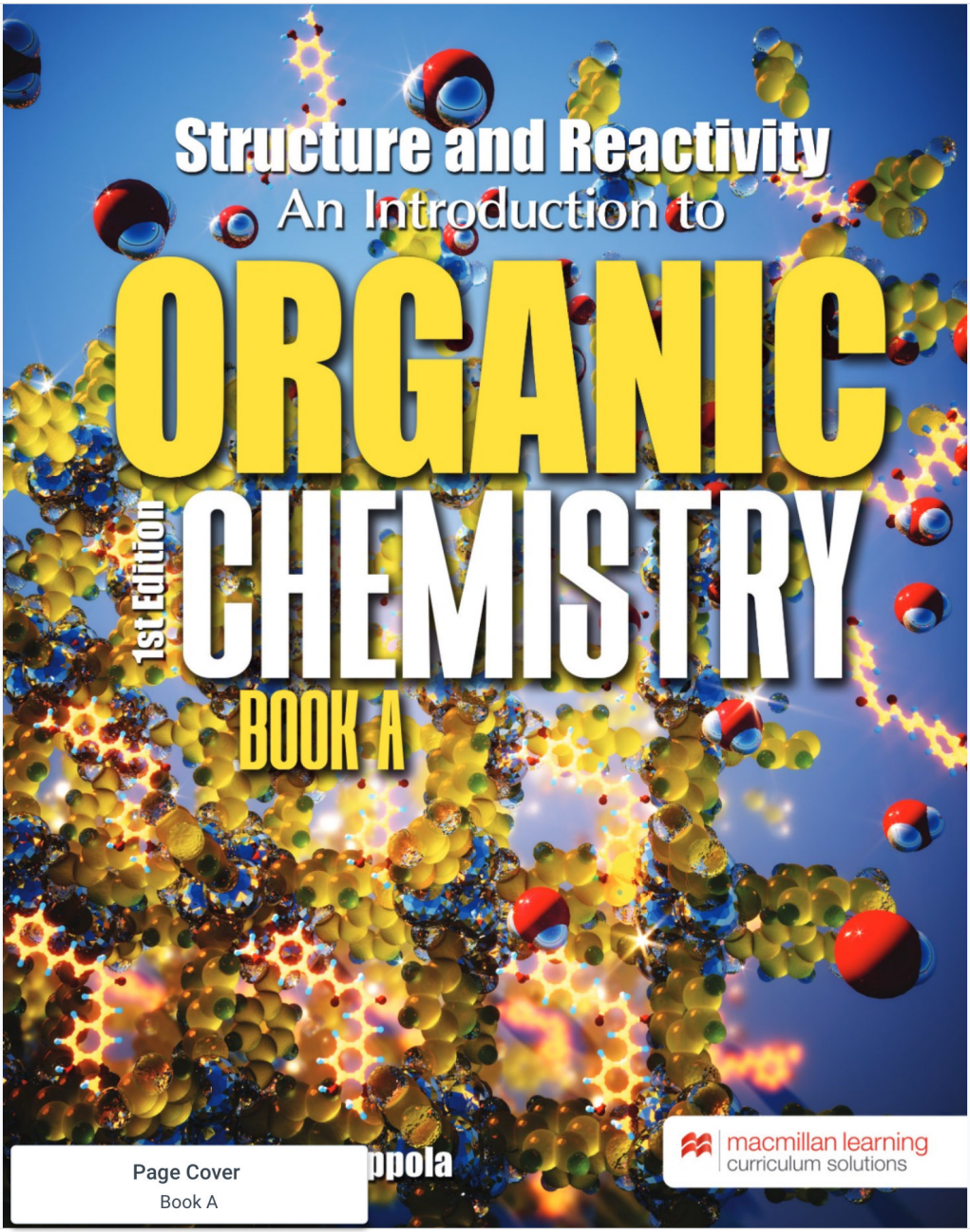

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Structure and Reactivity:
An Introduction to Organic Chemistry

Book A: Structure and Bonding

CH 01 Introduction to Structure and Reactivity of Organic Compounds
CH 02 Organic Molecular Structure and Properties
CH 03 Reactions of Organic Compounds as Acids and Bases
CH 04 Physical Organic Chemistry: Energetics and Mechanism
CH 05: Stereoisomerism of Organic Molecules
CH 06: Conformational Analysis of Organic Molecules

Book B: Introduction to Reactivity

CH 07 Substitution and Elimination Reactions of Polar Sigma Bonds
CH 08 Electrophilic Addition I: Brønsted Acids
CH 09 Electrophilic Addition II: Halogenation, Oxidation and Reduction Reactions
CH 10 Aromaticity and Electrophilic Aromatic Substitution Reactions

AP 01 Useful Expectations from General Chemistry
AP 02 Nomenclature of Organic Compounds I: Alkanes, Halides, & Alcohols
AP 03 Nomenclature of Organic Compounds II: Stereoisomers
AP 04 Nomenclature of Organic Compounds III: Alkoxy Groups, Alkenes & Alkynes

Book C: Carbonyl Reactions, Transformations, and Synthesis

CH 11 The Chemistry of Alcohols and Epoxides
CH 12 Nucleophilic Addition Reactions of Aldehydes and Ketones
CH 13 Nucleophilic Substitution Reactions of Acids and Acid Derivatives
CH 14 Nucleophilic Reactions of α-Carbon Acids

AP 05 Nomenclature of Organic Compounds IV: Aldehydes, Ketones, Thiols, and Sulfides
AP 06 Nomenclature of Organic Compounds V: Acids and Acid Derivatives
AP 07 Spectroscopic Determination of Organic Structures: UV and IR
AP 08 Spectroscopic Determination of Organic Structures: MS
AP 09 Spectroscopic Determination of Organic Structures: NMR

Book D: Special Topics

CH 15 The Diels-Alder Cycloaddition Reaction
CH 16 The Chemistry of Carbohydrates
CH 17 The Chemistry of Amino Acids and Proteins
CH 18 Bio-Organic Catalysis and Synthesis: Introduction to Enzymes
CH 19 Advanced Topics in Organic Reactions
CH 20 Frontier Molecular Orbitals and Pericyclic Reactions

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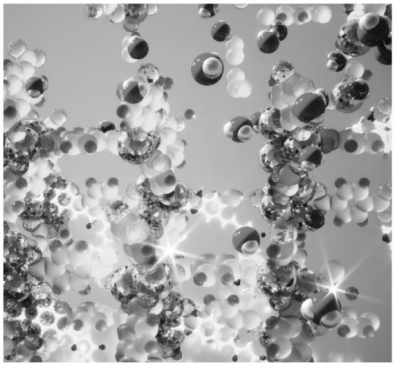
Structure and Reactivity

An Introduction to Organic Chemistry | Book A



First Edition

Structure and Reactivity: An Introduction to Organic Chemistry is a 4-book series that provides a student-centered approach to the first-year undergraduate course in Organic Chemistry.

The Study Guide for this textbook contains all of the answers to the three types of question sets in all four of the books: Practice Questions within the chapters, Chapter Questions at the end of the chapters, and Exam Questions after every block of 3–4 chapters that align with the undergraduate course at the University of Michigan (Ann Arbor). You are free to access these answers openly, at no charge, at the following URL:

https://mnv-media.s3.amazonaws.com/hm-media/coppolaABSG/index.html

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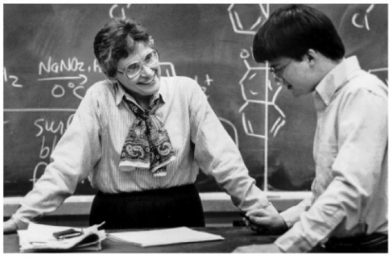
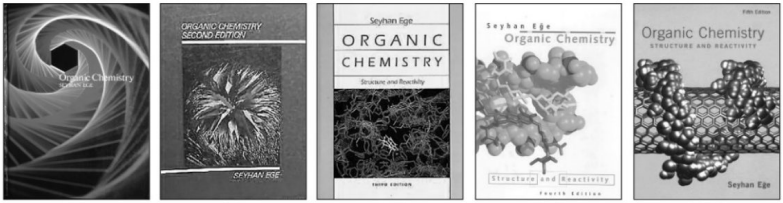


Seyhan N. Eğe (1931–2007)

As the author of this textbook, I draw from decades of teaching experience in courses that have enrolled nearly 100,000 students. This book reflects the essence of the introduction to organic chemistry, Structure and Reactivity, used by the faculty instructors in the department of chemistry at the University of Michigan (Ann Arbor); a course which, in 1989, became our standard first-year college chemistry course for students with a reasonable high school background. The texts we used for nearly four decades, the five editions (1984–2003) of Organic Chemistry, authored by the late Seyhan N. Eğe, who was a dear friend, serve as an inspiration for the current work. She was an inspiration. The book you are reading, as well as these predecessors, captures the singular experience of its respective author in combination with the constant evolution in the way the organic chemistry faculty at the University of Michigan think about teaching the introductory course.



1984 1989 1994 1998 2003

"Organic Chemistry" by Seyhan N. Eğe (1E, 1984 through 5E, 2003)

My own baseline knowledge of and love for organic chemistry derive from my undergraduate research advisors at the University of New Hampshire (Robert E. Lyle, Gary R. Weisman) and my PhD advisor at the University of Wisconsin-Madison (Barry M. Trost, Stanford University), as well as the outstanding organic chemistry instructors I had at UNH (Paul R. Jones, James D. Morrison) and UW (Edwin Vedejs, Charles Casey, Harlan Goering). At the University of Michigan, whose faculty I joined in 1986, my most influential teaching mentors were Seyhan N. Eğe, as I said, and Richard G. Lawton, both of whose clever minds were wide open to a constant give-and-take conversation about how to teach organic chemistry.

Over the course of nearly 40 years, my organic chemistry colleagues have readily engaged in a collective conversation about teaching this subject, including a few hundred junior and senior undergraduate students who have been the primary instructors for the Honors option in our organic chemistry courses. As an author, I take all the blame for everything that could be stated better throughout this text. And the credit for all the ideas for teaching this subject contained in these pages is shared gratefully and liberally with everyone whose minds I have collided with throughout my lifetime.

I am immensely indebted and grateful beyond words to the small group of dear friends and colleagues eedback on the drafts of these chapters. All of them have in common

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(well, in addition to knowing me) various degrees of experience and perspective in teaching organic chemistry at the University of Michigan and elsewhere, so they were steeped in the richest resource imaginable to me: insider knowledge and experience. Their open and frank responses were always spot on, and the resulting manuscript is only better for their observations, suggestions, and critiques.

I have asked them to say a few words and share a favorite recipe.

William H. Pearson

I met Will in 1978 when we both entered graduate school at the University of Wisconsin-Madison. He is my oldest and dearest friend.

"I grew up in North Carolina and Florida, obsessed with bicycles and surfboards. I received a BS in Chemistry from the University of North Carolina, where I was captivated by first semester organic chemistry. Stereochemistry blew my mind, as did the realization that organic chemistry relied heavily upon drawing chemical structures, which fit nicely with the part of my brain that likes to doodle. I did undergraduate research with Ernest Eliel, then headed to the University of Wisconsin to earn my PhD, where I became fast friends with Brian Coppola. We shared a fume hood in Barry Trost's group, and much to our mutual delight, both became professors at the University of Michigan. As a faculty member, I discovered something fundamental about my nature: I love to delve deeply into complex and interesting subjects and share what I've learned with others. Teaching at UM fit my nature, especially with Brian, who catalyzed a seismic shift in how chemistry is taught and learned at UM and elsewhere. We spent countless hours, whether at the gym or at coffee shops, talking about teaching organic chemistry."

"After many great years at UM, I left to try some new things. I helped grow a small chemistry company, became an independent chemistry consultant, added leadership coaching to my repertoire, and delved into hobbies and other activities outside of science. Racing sports cars at tracks around America has been a big passion, as has mountain biking and road biking. Lately, I can be found hiking in the mountains of North Carolina. I have also been exploring my creative side through drawing and painting, which I fully intend to teach at some point."

Will's Recipe: *Will's Perfect Pasta*

I had something like this long ago at a restaurant in Ann Arbor and decided to make my own version. My friends like it. Despite being an organic chemist, I don't measure anything when I make this dish. Just eyeball it.

Reagents: chicken breasts; marinade; shallots, chopped; olive oil; asparagus, trimmed; black olives, sliced; sun-dried tomatoes, diced (I like the ones that are packaged in olive oil); penne pasta; parmesan cheese, grated.

Experimental procedure:

1) Marinate some chicken breasts in something tasty. I use Soy Vay Veri Veri Teriyaki Marinade (but use your favorite). Grill the chicken and slice it into 1/4-inch thick strips.
2) Cook the pasta al dente, rinse briefly with cool water to stop the cooking, and toss with a little olive oil.
3) Steam or grill the asparagus to your preferred doneness. I just wrap it in a moist paper towel and briefly microwave it until it's deep green and a bit crisp. Chop into 1- to 2-inch pieces.
4) In a large cooking vessel (large enough to hold everything), saute the shallots in olive oil until they start to brown.
5) Add the chicken, mix, and warm.
6) Add the asparagus, olives, sun-dried tomatoes, and pasta; mix to coat everything. I add more olive oil at this

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point to bring everything together with the right consistency. Add salt and pepper to taste. You can heat the mixture up a bit if desired, but I usually don't—I like this dish slightly warm, but not hot.

7) Plate and top with grated parmesan cheese.

Alan L. Kiste

"When I'm not discussing the fundamental nature of the universe with my students, I spend my time singing in various ensembles on the Central Coast, walking the doggo, enjoying sci-fi/fantasy TV/movies, plotting my next tattoo, or playing around in the kitchen."

"I received my BS from Calvin College in Grand Rapids, and an MS (Macromolecular Science), MA (Education), and combined PhD (Chemistry & Education), all from the University of Michigan. I joined the faculty at California Polytechnic State University in 2011."

Alan L. Kiste and Kili (who say "it's important to coordinate your attire")—I met Alan in 1993 when he was a graduate student in the department. He has a cool and calm demeanor that served him well when he took a break from graduate studies to become a high school teacher, before returning to the first-ever self-designed PhD program that combined research in chemistry and in education.

Alan's Recipe: *Holiday Marshmallows*

Reagents: 3 packages unflavored gelatin; 1 cup water, divided into halves; 12 ounces granulated sugar; 1 cup golden syrup; 0.25 teaspoon kosher salt; 1 teaspoon vanilla extract (or other flavoring of your choice); 0.25 cup powdered sugar; 0.25 cup cornstarch; 2–3 candy canes or a handful (~1/2 cup) of hard red & white peppermint candies; Nonstick spray.

Lab Equipment: Stand mixer with whisk attachment; 9 X 13" baking pan; Food processor or blade-type coffee grinder; 1-gallon zip-top bag; Digital or candy thermometer; Saucepan; Kitchen shears or pizza cutter.

Experimental procedure:

1) Break the candy canes into pieces or put the handful of peppermint candies in a food processor or a clean blade-type coffee grinder and blitz until you get the texture of powdered sugar. Combine with the powdered sugar and cornstarch in a 1-gallon zip top bag.
2) Place the gelatin into the bowl of a stand mixer fitted with a whisk attachment, along with 0.5 cup of the water. Stir gently to combine and to hydrate the gelatin.
3) In a small saucepan combine the remaining 0.5 cup water, granulated sugar, golden syrup. Heat on med-high heat, cover and allow to cook until the sugar dissolves. Uncover, clip a thermometer onto the side of the pan and continue to cook until the mixture reaches 116 °C (240 °F), ~10 min. Temperature is crucial here, make sure you're measuring the temperature of the sugar/water mixture and not the temperature of the pan. Do not go more than a degree or two over the target temperature. Once the mixture reaches this temperature, immediately remove from the heat.
4) Turn the mixer on low speed and, while it's running, slowly pour the sugar syrup between the side of the bowl and the whisk into the gelatin mixture. Technique is crucial here. If you pour the super-hot sugar lava onto the cold mixing bowl, it will seize up and not form marshmallows. If you pour the sugar mixture onto the whisk, tiny droplets of sugar lava will be thrown around the room, some of them landing on your face. Once you have added all of the syrup, increase the speed to high. Whip until the mixture becomes very thick and is warm, spreadable, but not too hot to work with, ~15 min. Add the vanilla during the last minute of whipping. I find it helpful to move to whisk up and down a few times during the whipping process to get maximum lift.
5) While whipping, lightly spray the baking pan with nonstick cooking spray. Add 0.25 cup of the sugar/cornstarch/peppermint mixture and run it around to completely coat the bottom and sides of the pan. Return the remaining mixture to the zip-top baggie for later use. Thorough coating is important! If you use too much cooking spray the coating; you want a light coating of oil covered by a light covering of sugar.

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6) Coerce the marshmallow fluff into the pan, using a lightly oiled spatula for spreading evenly. Dust the top with enough of the remaining sugar/cornstarch/peppermint mixture to lightly cover; save the rest for later. Allow the marshmallows to sit uncovered for at least 4 hours and up to overnight, uncovered.
7) The next day: Dust a cutting board with the sugar/cornstarch/peppermint mixture. Turn the marshmallows out onto the cutting board and cut into 1" strips using kitchen shears dusted with the confectioners' sugar mixture. Cut each strip into 1" marshmallows and drop each into a zip-top baggie containing the powdered sugar, cornstarch, and peppermint sugar. Shake the baggie to coat all sides of each marshmallow. Remove them from the baggie and do the next strip of marshmallow. Store your glorious marshmallows in an airtight container, with waxed paper between layers, and each layer lightly dusted with the sugar/cornstarch/peppermint mixture to prevent sticking.

Notes: This is based on Alton Brown's marshmallow recipe, but he makes the rookie mistake of forgetting about British golden syrup, which is mostly unknown in the U.S., but is absolutely essential to getting real flavor. You can substitute light corn syrup, but it won't be as good. Do yourself a favor and go online and find a respectable brand of British golden syrup. The sugar dusting is a perfect way to add more flavor: use peppermint! Or, instead of peppermint (which is brilliant in hot chocolate or s'mores), you could use cocoa powder, or really any other flavor you want. I've done some with a very small amount of some blitzed savory spices (cinnamon, cloves) and they've turned out well. Because we're using gelatin, these are not vegetarian. The sugar/corn starch/peppermint mixture is highly hygroscopic so when storing in the zip-top baggie, squeeze all the air out of the bag before storing, even overnight.

Jason K. Pontrello

"I've always viewed the world with simple complexity, logically, coherently; I was always interested in art classes, science, and playing the piano. I managed to intersect multiple potentially diverse paths in the field of organic chemistry and its applications. Nothing compares to standing in front of a classroom of students, explaining a basic concept like resonance or NMR, telling a story through a reaction mechanism that plays like music in my head, and drawing molecules on a board with precision and speed that elicits countless comments about my abilities to explain and draw on course evaluations. And undoubtedly, practice running experiments in lab translates into skill in a kitchen."

Jason is a truly gifted classroom instructor whom I first met as a student in my classes in 1994. He taught with me for three years in various capacities.

"I received my BS from the University of Michigan, Ann Arbor, in 1998 and a PhD from the University of Wisconsin, Madison, in 2004. After 10 years of faculty positions, I became a pharmaceutical company contractor while balancing the home care for four sons."

Jason's Recipe: *Pontrello Tiramisu*

Reagents: 8 oz semisweet chocolate, melted, + grated for topping; 8 egg yolks, 4 egg whites; ½ c + 6 Tbs sugar; ½ tsp vanilla; 16 oz mascarpone cheese; 3 tsp powdered instant espresso; 2 c heavy cream; 7 oz savoiardi; ¼ c Amaretto Disaronno.

Experimental procedure:
Chocolate Layer (steps 1–4)

1) Melt 8 oz semisweet chocolate in double boiler
2) In round bowl over double boiler, whisk the following constantly until mixture is pale yellow and light and fluffy, about 4 minutes: a. 8 egg yolks; b. ½ c sugar; c. ½ tsp vanilla
3) Gently fold in warm melted chocolate.

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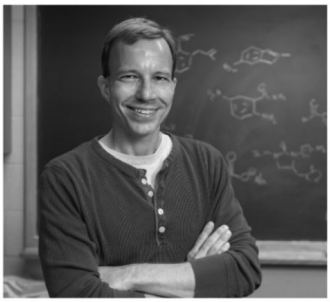
4) Whip 4 egg whites and gently fold into warm chocolate mixture.
5) Mascarpone Layer: In a large bowl, whisk: a. 16 oz mascarpone cheese; b. 2 tsp instant espresso; c. 1/3 c water; d. 3 Tbs sugar.
6) Cream Layer: Whip 2 c heavy cream with 3 Tbs sugar.
7) Cookie Layer: Combine ¼ c Amaretto Disaronno, ½ c water, and 1 tsp powdered instant espresso in a small, flat baking dish. Dip each side of 7 oz savoiardi quickly into liquid and arrange in glass serving bowl.

Assemble seven layers: 1. cookie (1/2 amount); 2. cream (1/2 amount); 3. chocolate (all); 4. mascarpone (all)—heavier than chocolate, put along edges and gently spread to center; 5. cookie (1/2 amount); 6. cream (1/2 amount); 7. grated chocolate to top

John P. Wolfe

"I am a Colorado native who received a BS degree from the University of Colorado in 1994, where I carried out undergraduate research with Prof. Gary Molander. I completed my PhD at MIT under the supervision of Steve Buchwald in 1999, and after postdoctoral research at UC Irvine with Prof. Larry Overman, I began my faculty career at the University of Michigan in 2002. I am an Arthur F. Thurnau Professor of Chemistry, and currently (as of 2021) Associate Chair for Undergraduate Education."



I met John in 2002 when he started his faculty career at the University of Michigan. Between us, he and I have shared a few decades of being Associate Chairs for the department, and I value greatly our constant dialogue.

John's Recipe: *Flexible Guacamole*

Reagents: 3 ripe avocados; 1 whole lime; 1 clove garlic, minced; 1/2 fresh jalapeno pepper, seeded and diced; 1/2 onion, diced; 1 roma tomato, seeded and diced; 3 Tbsp chopped cilantro; 1/2–1 tsp salt; optional: a few dashes (or more, if you are like me) of chipotle Tabasco sauce, to taste. All of ingredients (other than avocados) can be adjusted up/down to taste.

Experimental procedure: Slice avocados lengthwise, remove seed and peel, and mash with fork. Cut lime in half, squeeze juice onto mashed avocados, stir to mix. Add remaining ingredients, chill 15–30 min. Serve with tortilla chips, tortillas, vegetable, pita bread, etc.

Justin P. Lomont

Justin is one of the most laid-back people I know. I first met him as a student in my classes in 2004. He taught with me for 3 years, including as my chief surrogate for a summer research program in China, where we brought up to 30 students a year from around the US to Beijing for 10 weeks of research experience. We were on Tiananmen Square together for the 20th anniversary of the 1989 protests.

"Like many others, I was drawn into chemistry from my first courses back in high school. I've always been excited at how chemistry organizes our understanding of the world by providing a conceptual framework for breaking down processes, materials, and life forms (etc.) into smaller systems that we can begin to analyze in a systematic way. I continue to be amazed by the diversity of the field, and its broad and deep connections with virtually every other area of scientific study. I view communicating and passing along knowledge as

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vital components of science. I've always enjoyed teaching, training, and working with young scientists throughout my education, and I hope to continue to take advantage of similar opportunities as a scientist in the biopharmaceutical industry. In particular, I'm intrigued by the interdisciplinary nature of scientific education, and how training in related fields (biology, physics, mathematics, computer programming, data science, and engineering, among others) is becoming increasingly important in a well-rounded chemistry education. Outside of chemistry, I enjoy travelling, playing with my dogs, golf, video games, time at the beach, and trying new foods."

"I received my BS in Chemistry from the University of Michigan, Ann Arbor, in 2008, and a PhD in Chemistry from the University of California, Berkeley, in 2014. I completed postdoctoral fellowships in Systems Biology and Biophysics at the California Institute of Technology and the University of Wisconsin, Madison, respectively, and began my independent career as a Senior Scientist in the biopharmaceutical industry."

Justin's Recipe: *Pepper Chili*

Reagents: 1.5 lbs ground beef (or turkey); 4 cloves garlic (crushed); 2 cups black beans (cooked); 2 cups red beans (cooked); 6 oz tomato paste (from can); 2 tomatoes (diced); 1 red onion (diced); 2 green peppers (diced); 1 yellow pepper (diced); 1 red pepper (diced); 3 jalapeño peppers (sliced); 1 cup yellow corn (cooked, optional); 1 tbsp brown sugar; 3 tbsp chili powder (add more/less to taste); 1 tsp garlic powder (add more/less to taste); salt & pepper, added to taste; hot sauce of your choice, added to taste. Toppings (optional): cheddar cheese, corn chips, green or red onions, sour cream, cilantro. Serve with fruit.

Experimental procedure: This is a very simple recipe to cook once you have the ingredients ready!

1) Brown ground beef (or turkey) in a large pot for ~10 minutes, or until cooked thoroughly. Add crushed garlic and cook for 1 minute. Drain if desired, but I recommend to not drain.
2) Add in the beans and all the vegetables, plus 2 cups water. Bring to a low boil and then simmer covered for ~1 hour, stirring occasionally.
3) Taste, then add in the chili powder, garlic powder, brown sugar (a secret ingredient recommended by my grandmother, also works well in mostaccioli), salt and pepper, and hot sauce, stirring and tasting to check flavor. Adjust with more spices as desired.
4) Allow to simmer an additional 30–45 minutes, then it's ready to serve!

Anne J. McNeil

"I first ran across this proverb after both my parents had passed away: *Be happy in this moment, for this moment is your life.* My siblings and I had just finished spreading their ashes in a river near our favorite childhood campsite, and I was reflecting on the ephemeral nature of life. We walked past a bench with this message engraved on it. It was so powerful. My mind is always juggling a bunch of work- and home-related thoughts (both past and future) and this message always reminds me to join the present moment and quiet the rest."

I met Anne in 2007 when she started her faculty career at the University of Michigan. Anne is a tireless champion for both the transformative power of education and for the strength to science and society that comes from participation by people with diverse backgrounds and experiences.

"I am the Carol A. Fierke Collegiate Professor of Chemistry and Macromolecular Science and Engineering at the University of Michigan in Ann Arbor, an Arthur F. Thurnau Professor and HHMI Professor. The overarching theme of my research to solve problems in ed to supporting and

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promoting people from groups that are historically underrepresented in the field, with several initiatives including the website, DiversifyChemistry.com."

"Prior to joining the Michigan faculty, I was a L'Oreal Postdoctoral Fellow in Prof. Tim Swager's group at MIT, where I developed oxidatively stable conjugated polymers. I received my PhD from Cornell University, where I worked with Prof. Dave Collum on the structure and reactivity of lithium enolates. And I received my BS in Chemistry from the College of William and Mary where I graduated with highest honors (based on a thesis with Prof. Rob Hinkle) and *summa cum laude*."

Anne's Recipe: *Peanut Butter Cup Tart*

Reagents: For the Graham Cracker Crust: 1 and 1/3 cups (139g) graham cracker crumbs (about 9 full sheet graham crackers); 1/4 cup (4 Tbsp; 60g) unsalted butter, melted; 2 Tablespoons (25g) granulated sugar. For the Filling: 6 Tablespoons (85g) unsalted butter, softened to room temp; 1 cup (120g) confectioners' sugar; 1 teaspoon pure vanilla extract; 1/8 teaspoon salt; 1 and 1/4 cups (315g) creamy peanut butter. For the Topping: 6 ounces (170g) semisweet, bittersweet, or milk chocolate; 2 Tablespoons (31g) creamy peanut butter.

Experimental procedure: I follow this recipe exactly as I found it, at the web site called sallysbakingaddiction.com.

1) Preheat oven to 350°F (177°C).
2) Make the crust: Stir the graham cracker crust ingredients together. Pour into a 9-inch tart pan and pack in very tightly. The tighter it's packed, the less likely it will fall apart. I recommend using the bottom of a measuring cup to pack it into the bottom and around the sides. Bake for 13–15 minutes or until very lightly browned around the edges. Remove from the oven and allow to cool for at least 20 minutes before adding the filling.
3) Make the filling: Using a hand mixer or a stand mixer fitted with paddle attachment, beat the softened butter on medium-high speed until completely smooth and creamy, about 2 minutes. Add the confectioners' sugar, vanilla extract, and salt and beat until combined, about 1 minute. Scrape down the sides and up the bottom of the bowl as needed. Add the peanut butter and beat until smooth and combined.
4) Spread filling evenly into cooled tart crust. Set aside as you prepare the topping.
5) Make the topping: Using a double boiler or microwave, melt the chocolate and peanut butter together until smooth. If using the microwave, stop and stir every 15 seconds until melted. Pour and spread over filling. (Optional: save 1–2 Tablespoons of the topping and drizzle it on top after the topping sets.)
6) Chill in the refrigerator, uncovered, for 4–6 hours (or up to 2 days) before slicing. If chilling for longer than 6 hours, cover it. This crust is crumbly no matter what, but chilling for 6+ hours helps the tart slice a little neater.
7) Cover leftovers tightly and refrigerate for up to 1 week.

Daniel J. Nassrallah

I met Dan in 2015 when he joined the department as a graduate student. He was enthusiastic, excellent, and thoughtful with everything he did with me, from his duties as a GSI, to contributing to a new course for undergraduate peer leaders, to being a super-duper member of the department's future faculty program.

"I find it important to remember (and hopefully encouraging to the students reading this) that at one point in my life I didn't realize 'normal people' could become professors. It wasn't until my sophomore year of college that I realized this could be a possibility for me. It was also my sophomore year when I met the woman who would later become my wife, as well as when I made the decision to follow Jesus Christ as my Lord and Savior. These three formative events all took place during college and have completely changed the course of my life. As you read this, I hope anything and can do anything you put your mind to. Good luck!"

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"I received a BS from the University of North Carolina, Greensboro, in 2014. After graduating, I went on to complete a PhD from the University of Michigan, Ann Arbor in 2020. After graduation, I moved to a fantastic postdoctoral experience that combines teaching organic chemistry and conducting research as the Donald J. Cram Assistant Adjunct Professor of Chemistry at the University of California, Los Angeles. My wife Hayley and I are just smitten with our daughter, Delia, who was born during our first year in LA."

Dan's Recipe: *Dan's One Pot Wonder*

This recipe kept me well fed throughout graduate school. I made a large pot very often during my 5 years at the University of Michigan. It is a simple procedure. I hope it will help other students endure the long Michigan winters (or wherever they are).

Reagents: 2–3 large chicken breasts; 2 15.5 oz cans black beans, rinsed
2 15.5 oz cans pinto beans, rinsed; 2 15.5 oz cans kidney beans, rinsed; 1 28 oz large can tomatoes; 1 15.5 oz can or frozen bag of whole kernel corn; 1 jar of your favorite salsa; 1.5 cups chicken broth.

Experimental procedure:

1) Add everything to a large pot and bring to boil.
2) Lower heat and let simmer for at least one hour, stirring occasionally.
3) Remove chicken breasts, cutting into pieces or shred (they should easily fall apart), add chicken back to the pot.
4) Garnish immediately before serving with sour cream, cheese, hot sauce, and/or avocado. Enjoy with tortilla chips on the side!

Jenna L. Manske

"On the first day of my undergraduate career, I sat down in Room 1800 CHEM at 8 a.m., began to learn organic chemistry, and have never stopped. My four years at the University of Michigan taught me the value of hard work, the importance of making and maintaining strong friendships, and of course, chemistry. I enjoy traveling, have a passion for teaching and mentoring, and have an absolute love of learning, chemistry, and research. To students enrolling in this course: I encourage you to have fun with the process of learning chemistry and find what you are passionate about and stick with it!"

"I received my BS in Chemistry from the University of Michigan, Ann Arbor, in 2020 and conducted undergraduate research with Professor John Wolfe. I then moved to California to pursue a PhD at the University of California, Berkeley, researching transition metal catalysis and mechanism with Professor John Hartwig."

I met Jenna in 2018 as an undergraduate student at the University of Michigan. She taught with me for two years and helped start up a wide array of programs for undergraduate science students. She reviewed, solved, and commented on all the questions from Chapters 1–10 (Books A and B).

Jenna's Recipe: *Grandpa Manske's Pancakes*

Reagents: 1 cup flour; 1 tablespoon sugar; 1 teaspoon baking powder; ½ teaspoon of salt; 1 cup of milk; 1 egg. And optional: ½ cup chocolate chips or blueberries or walnuts or chopped apples (microwave for ~30 seconds) and cinnamon.

Experimental procedure:

1) Combine dry ingredients in one bowl and mix, then add the milk and egg and stir until mixture is very homogenous. Fold in optional ingredients!
2) Oil a pan, turn stovetop to medium and cook to whatever size and shape you want.
3) Serve with butter, fruit, syrup, Nutella, whipped cream… use your imagination!

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Drew Tarnopol

"Telling people that I study both Chemistry and Middle Eastern Studies generally garners one of two responses: either 'Oh really… why?' or just a puzzled, concerned look. I don't entirely blame them; there is a common conception that STEM and Humanities, like aqueous and organic layers, never mix. But anyone who's carried out an LLE knows it's easy to form a pesky emulsion. In the same way, my experiences in both fields have overlapped and influenced each other in different ways. My piece of advice for any aspiring chemist is to remember: Chemistry's primary practitioners and beneficiaries are human beings, so you'll work, learn, and be your best by observing and listening to those around you."

I met Drew in 2020 as an undergraduate student at the University of Michigan. He also taught with me for two years and has an excellent breadth of interdisciplinary interests that give him a uniquely well-rounded outlook on life. He reviewed, solved, and commented on all the questions from Chapters 11–20 (Books C and D).

Drew's Recipe: *D-man's Shak(shuka)*

Reagents: 4 fresh tomatoes (diced) or 28 oz. can crushed tomatoes; 1 medium onion (chopped); 6 cloves garlic (minced); salt; pepper; 1 tbs. Ras el Hanout*; ½ tbs. sweet paprika; ½ tbs. smoked paprika; Harif* (this can be any MENA spice paste, e.g., tzchüg, harissa, shatta); 4 large eggs; olive oil. Optional: feta cheese, warm pita bread.*

** I get these from my local Middle Eastern market*

Experimental procedure:

1) In a medium/walled pan, preheat the oil on medium-high heat. Add the onion and cook until translucent. Add the garlic and cook about ~1 min, then add the Ras el Hanout. Cook another minute until fragrant.
2) Add the tomatoes, followed by the two paprikas. Add the Harif according to personal preference. Lower the heat to a simmer and allow the tomatoes to cook down and reduce until thick enough to form a nice crater with a spoon (this part can take a while depending on the water content of the tomatoes). Season with salt and pepper to taste).
3) Once the tomatoes have thickened and reduced, form 4 small craters and add one egg into each. Cover the pan to cook the egg evenly (~10 minutes).
4) Once the eggs have cooked, season each egg with a little salt. Top off with some feta if desired. This dish goes very well with some fresh, warm pita pockets, but any nice bread or toast will do.

I am also deeply indebted to the individuals who helped me turn a manuscript into the physical form of a book. The production was handled single-handedly by Jody Toth, with whom I have worked for more than 20 years. She brings a keen aesthetic sense to everything she touches, and every recommendation has made the final version better. My proofreader, Jama Carter, is a true detective of words and other symbols. I envy greatly her attention to detail and consistency that I cannot ever come near. I thank everyone at Hayden-McNeal, past and present, for our long-standing relationship, and particularly Eric Gallipo for his role as my primary contact and managing editor.

Dedication

To those who have taught and led by example: Roald Hoffmann, James W. Hovick, Mary T. Huber, Joseph S. Krajcik, Robert L. Lichter, Wilbert J. (Bill) McKeachie, Bassam Z. Shakhashiri, Lee S. Shulman, Pratibha Varma-Nelson, and members of the 1998 CASTL Scholars (aka The Pew Few).

Brian P. Coppola
16 June 2021

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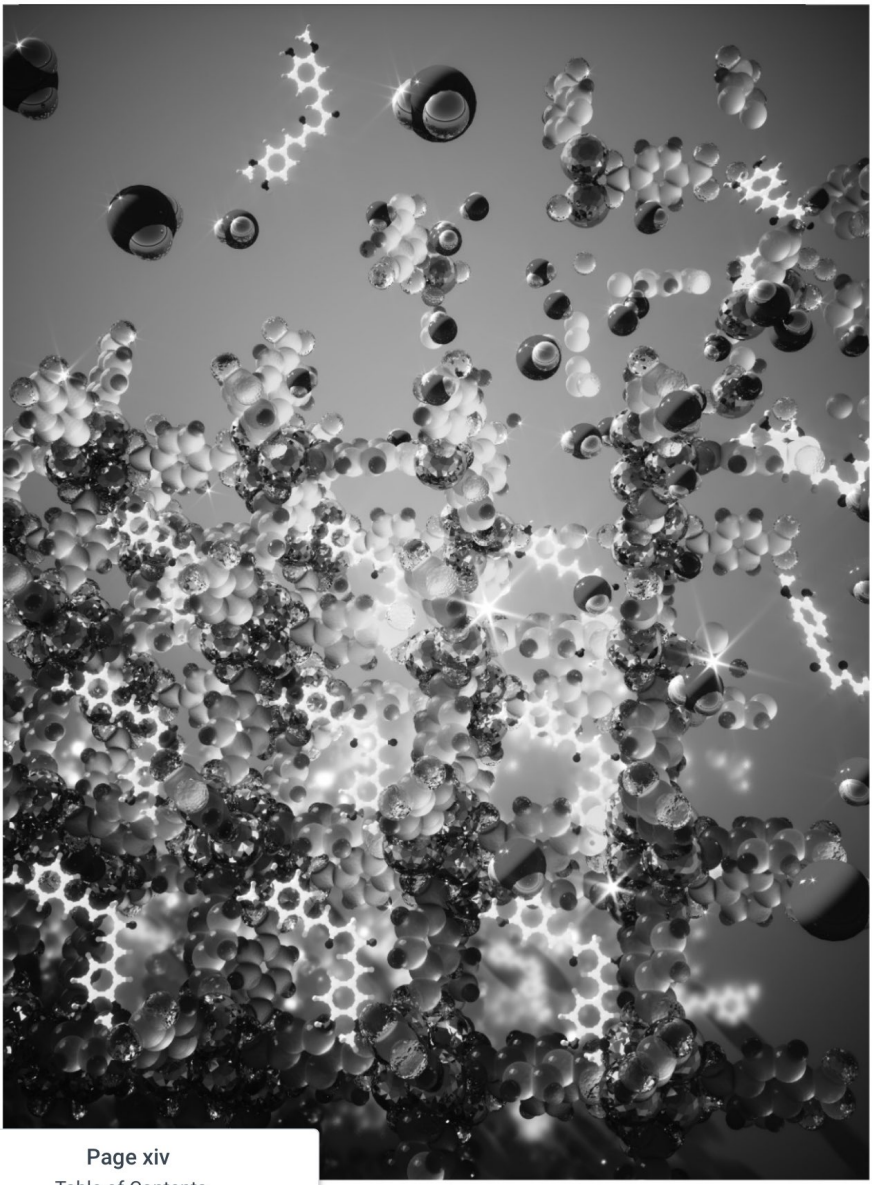

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Book A

On the Cover

Curcumin, present in the spice turmeric, has potential therapeutic benefits as an antioxidant, anti-inflammatory, antitumor, antihyperglycemic, antimalarial, antibacterial, antiviral activities, and against Alzheimer's disease. However, its poor water solubility has limited its development as a medicine, which creates a drug delivery problem to solve.

One strategy to overcome the drug delivery dilemma uses a water-reactive metal-organic framework (MOF) as a drug carrier. As the name implies, a metal-organic framework is a cage with pores in which the drug candidate can sit. In the aqueous environment of the human body, the MOF carrier will self-destruct, leading to the release of the drug in a useful therapeutic dose.

Research on drug delivery using MOFs is carried out by the research group led by Professor Adam J. Matzger at the University of Michigan.

Kuthuru Suresh, Adam J. Matzger, "Enhanced Drug Delivery by Dissolution of Amorphous Drug Encapsulated in a Water Unstable Metal–Organic Framework (MOF)" *Angewandte Chemie International Edition*, **2019**, *58*, 16790.

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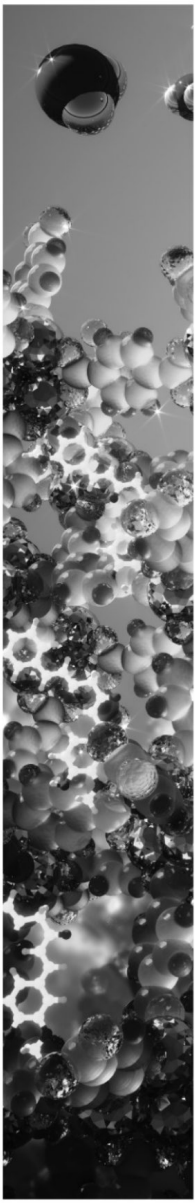

CHAPTER 1

Introduction to Structure and Reactivity of Organic Compounds

Setting the Stage: The Liberal Art of Organic Chemistry

1.1 Why People Invented Molecules
- A. Chemistry Before Molecules
- B. Elemental Composition
- C. The Need for Molecular Structure and the Invention of Isomerism
- D. Models for Chemical Affinity and Bonding

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CHAPTER 1

Introduction to Structure and Reactivity of Organic Compounds

Setting the Stage: The Liberal Art of Organic Chemistry

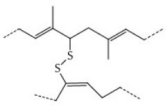
Welcome to your study of organic chemistry.

Organic chemistry courses differ significantly from the previous science courses that nearly all students have taken. Yes, the subject matter is new and unfamiliar, but the course is also not titled "General" in the way that introductory science courses are typically listed: General Chemistry, General Biology, and General Physics.

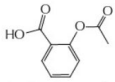
The "general" introductory sciences courses are structured as surveys, introducing many topics that might be only loosely connected. From one week to the next, sometimes from one day to the next, there is a new topic that may or may not build upon the previous one. An introduction to organic chemistry is structured differently than these survey courses because organic chemistry is a single, specialized area of chemistry.

Organic chemistry is an authentic sub-discipline within chemistry. As such, the individuals who teach it are likely to have been trained as organic chemists, and they have a deep depth of understanding to draw from because organic chemistry is an area of exciting and active research. Every year, hundreds of thousands of pages of new discoveries involving organic chemistry are published, in areas ranging from new materials for manufacturing objects that are lighter, cheaper, and more durable than before, to medical equipment and other biosensors used in hospitals, mobile devices, and even clothing; from new batteries and other methods for generating and storing energy in safe and sustainable ways, to new pharmaceuticals that can combat genetic diseases and the rapidly evolving viruses and bacteria that threaten human health (Figure 0101).

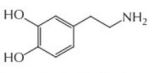
Figure 0101
Organic chemistry in the world.

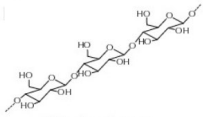

Rubber soles on shoes

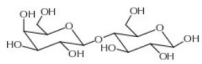
Caffeine in coffee


Aspirin in a packet

"Inside Leopold's" (24 x 36", oil on canvas, 2013). An annotated painting from the author's collection, used with permission of the artist, Stephen Kasun.


Dopamine in the brain


Wood and paper


Lactose in milk

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A common experience in general science survey courses is that many topics are all covered at more or less the same depth, with new topics either independent or marginally dependent on the previous ones. In contrast, learning organic chemistry is likely to be the first experience you have with learning science in a way where the understanding is consistently built up from a foundation, where understanding the new topics are completely dependent on understanding the previous ones.

As a genuine area of science, organic chemistry provides an authentic look at one small slice of the way humans think about understanding the world. As you move from course to course during your education, you should begin to see how different people view the world, and how they ask and answer questions about how the world works. Together, this collective understanding is an important way to think about what a Liberal Arts education means.

Perhaps the single greatest benefit from a successful Liberal Arts education is a person who can take what they learned in an area outside of their main interests and make use of it. Future scientists who only take science courses will only learn how scientists think about and solve problems. Historians, psychologists, and artists look at the same world that chemists do, but they approach asking questions and solving problems in quite different ways than chemists.

The promise of the Liberal Arts experience is that a future scientist who also learns about history, psychology, and art, will also learn enough about how problems are solved in those areas and potentially bring new thinking and new ideas to solving the problems that science has yet to solve—and vice versa! This promise is the core premise of why we embrace diversity of background, experience, and ideas: it provides a chance to innovate the thinking, the methods, and the experiences from inside of the boundaries of one area by including, borrowing, and adapting the ideas from what the rest of the world has learned outside of that area.

There are many descriptions for the goals of a Liberal Arts education. A simple list, suggested by Arthur H. Camins, the 2011–2016 director of the Center for Innovation in Engineering and Science Education at the Stevens Institute of Technology, was published in *The Washington Post* (08/08/2012). Camins argues that educated people ought to be

- comfortable with ambiguity.
- skilled in the search of uncertainty.
- experienced with learning from failure.

Camins recognizes that university-educated students need more than a prescribed set of facts to recall and repeat; instead, they need to be educated in ways that prepare them to seek out and discover new knowledge and to create innovative solutions for the difficult problems that need to be solved.

Roger Smith, the former CEO of General Motors, delivered an address at the University of Michigan in 1985 in which he outlined a longer, but generally comparable list. Some of the highlights from his list include these:

Individuals successfully graduating from a Liberal Arts education

- are trained to recognize recurring elements and common themes.
- are trained to see relationships between things that may seem different.
- are trained to combine familiar elements into new forms.
- learn to arrange their thoughts in logical order, to write and speak clearly and economically.
- learn to tolerate ambiguity and bring order out of apparent confusion.

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- are accustomed to a relatively unstructured and unsupervised research and discovery process and feel comfortable with nonconformity.
- learn about the kind of creativity that leads to visionary solutions.

In reflecting on Liberal Arts values, neither Camins nor Smith talk about learning how to take a second derivative, balance stoichiometry questions, translate Deledda, compose a song, or write an editorial. They do not prescribe that any particular subject area is better or worse at accomplishing these goals than any other. Instead, they argue that the learner creates their educated self through an authentic and diverse exposure to different ideas from the expertise of people who are currently thinking about those ideas.

Done well, a study of organic chemistry can contribute to your education by providing the experience of learning about how our current thinking has evolved, how the simple inventive creativity of people solved some interesting problems, how there are plenty of questions that are not at all settled, and how we deal with them.

Welcome to your study of organic chemistry.

1.1 Why People Invented Molecules

A. Chemistry Before Molecules

Ideas evolve. In this first section and throughout the book, some of the context in which chemistry evolved will be integrated into the text, whether it is through history, word origins, or stories about the scientists who did the work. You are not likely to be tested on this specific information, but do not skip it—the deliberate decision about what to include is intended to enhance your understanding of the subject.

Humans have been doing chemistry for a long time. Cooking food has been around for an estimated 2 million years, and all primates generally enjoy the deliciously browned bits of meats, breads, and fried foods that come from heating proteins and sugars together (called the Maillard reaction). Finding and using medicinally useful plants is thought to at least go back to the Neanderthals, 50–60,000 years ago, and the deliberate isolation of biologically active substances appears in the earliest written records from 4–5,000 years ago. Useful metallurgy started 8–10,000 years ago, and we accordingly describe some ancient eras as the Bronze Age, Iron Age, and so on.

Curiosity about matter and its description appear in both ancient Western (Greek) and Eastern (Indian) cultures 2,500–3,000 years ago. In the West, atomism was rejected, in great part, because noncontinuous matter required accepting emptiness, or a void, between atoms (and "nature abhors a vacuum").

The renaissance of atomism did not happen until the rise of mathematical physics during the age of Descartes, Galileo, and Newton (ca. 1550–1700 CE). Until then, chemistry had been kept alive through medicine and metallurgy, in the alchemical traditions that began with the ancient Egyptian and Greek civilizations and persisted throughout the world for 4,000 years, and always strongly connected with religious traditions, from Taoism, Jainism, and Buddhism to Islamism and Christendom.

As humans began to think about the particulate nature of matter again, many of the old ideas re-emerged. For example, people projected their macroscopic understanding of the world onto the particles. A common model for how small particles could cling together was through a hook-and-eye model (pretty

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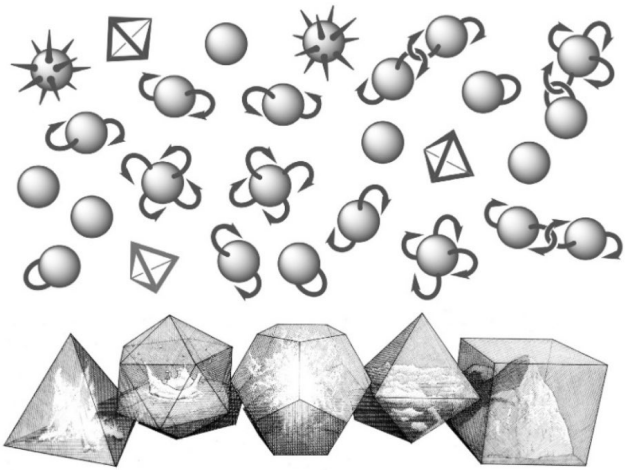
much the same way Velcro works), while the reason for why things felt severely cold or severely hot was because the particles were pointy and were simply harmful in the same way a knife or needle might be (Figure 0102).

Figure 0102
Images of ancient ideas about particles.



Top: From Democritus (c. 460–370 BCE) to John Dalton (1766–1844), the atomic model reflected a physical interpretation from the macroscopic world of spheres, points, hooks, and eyes as a way to imagine the unseen world of atoms and how they joined together. Bottom: "Kepler's Elements" Gerhard, 2020, [5 x 16", ink on board]. Copyright by the author. Johannes Kepler, in the "Harmonices Mundi" (The Harmony of the World; 1619), discusses the harmony and congruence in geometrical forms and physical phenomena. Kepler extrapolated Platonic philosophy to create some of the most iconic drawings in the history of chemistry, in which he integrated contemporary ideas about the five basic elements into the properties of the five physical forms of the Platonic solids. The pointy tetrahedron represents the sharpness of fire, and so also then the particles of fire are tetrahedral. The easily packed cubic form contains the properties of the earths (solids). The octahedral form is associated with air (gasses), and the highly mobile icosahedron with water (liquids). The 12-sided and spherical dodecahedron is associated with the aether of the heavens, one side (clearly) for each sign of the zodiac with the blazing sun in the center (Kepler is credited as being one of the first prominent astronomers who embraced fully the Copernican heliocentric model of the universe).

B. Elemental Composition

Within about 100 years, the idea of an irreducible unit of matter (atoms; Robert Boyle, 1661) evolved and resulted, by 1789, in the first published list of 33 elements (Elementary Treatise on Chemistry, Antoine Lavoisier). Over the next 20–40 years, that number grew to 49.

Historically, the origin or property of a substance often provided its name. The word gold recurs in many different languages and invariably means "gilded" or "shiny" and is strongly associated with the sun. The term acid is also quite common across different languages, and uses a word associated with the "acrid" taste of a substance such as vinegar (Greek: *oxys*; French: *acide*; German: *säure*). Carbon comes from *carbo*, which is a Latin word for coal or charcoal. The word ammonia derives from "the salt of Ammon/Amun" (sal ammoniac), the mineral we now call ammonium chloride, found around the ancient Temple of Amun, likely formed from the decomposition of camel dung. And the word chlorine contains one of its principal properties, that is a green gas (from *chloro*, a Greek word that means "a light green or greenish-yellow color"). Fluorine, named for the mineral fluorite in 1812, derives from the fact

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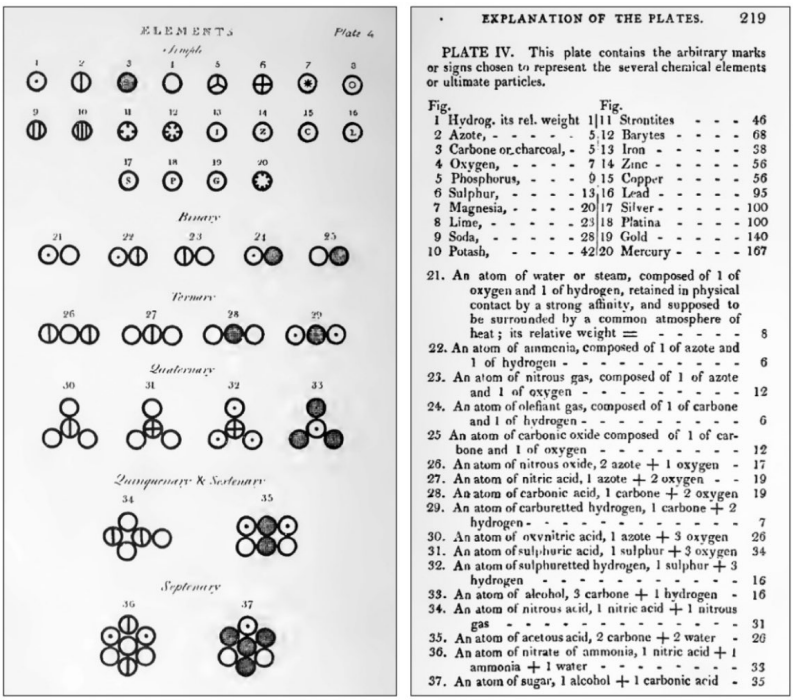
that the mineral, in the 1500s, permitted a greater flow of liquid iron metal during smelting. Hence, the mineral was originally named fluorite based on the Latin verb, *fluere*, meaning "to flow."

Useful chemical reactivity is often captured in the names of elements. The familiar "-gen" suffix comes from "genes" (meaning a "bringer of" something, as in genesis). Hydrogen (the bringer of water), oxygen (the bringer of acids), and the general term halogen (the bringer of salts) are all names that were invented to convey scientific information. Today, we convey specific information about the chemical composition of substances. Names such as "pentane" and "hexane" and "octane" are telling the reader that there are "five" and "six" and "eight" (of something) associated with these materials.

Lavoisier's 1789 text also outlined the first definitive summary of the experimental methods for elemental analysis (the elemental composition, by weight percent, of substances, e.g., 38% carbon, 5.5% hydrogen). John Dalton produced a table of elemental symbols, based on circles with different inscriptions, and proposed that compounds of these elements could be represented as the combination of atoms (Figure 0103). During the same 20- to 40-year time frame, through the early 1800s, the concept of different atomic weights also emerged.

Figure 0103
Dalton's elements and molecules.


ELEMENTS
Plate 4
Simple
Binary
Ternary
Quaternary
Quinquenary & Senary
Septenary
EXPLANATION OF THE PLATES. 219
PLATE IV. This plate contains the arbitrary marks or signs chosen to represent the several chemical elements or ultimate particles.
Fig. Fig.
1 Hydrog. its rel. weight 1 11 Strontites - - - 46
2 Azote, - - - - - 5 12 Barytes - - - - 68
3 Carbone or charcoal, - 5 13 Iron - - - - - 38
4 Oxygen, - - - - 7 14 Zinc - - - - - 56
5 Phosphorus, - - - 9 15 Copper - - - - 56
6 Sulphur, - - - - 13 16 Lead - - - - - 95
7 Magnesia, - - - - 20 17 Silver - - - - - 100
8 Lime, - - - - - 23 18 Platina - - - - 100
9 Soda, - - - - - 28 19 Gold - - - - - 140
10 Potash, - - - - 42 20 Mercury - - - - 167
21. An atom of water or steam, composed of 1 of oxygen and 1 of hydrogen, retained in physical contact by a strong affinity, and supposed to be surrounded by a common atmosphere of heat; its relative weight = - - - - - 8
22. An atom of ammonia, composed of 1 of azote and 1 of hydrogen - - - - - - - - - - 6
23. An atom of nitrous gas, composed of 1 of azote and 1 of oxygen - - - - - - - - - 12
24. An atom of olefiant gas, composed of 1 of carbone and 1 of hydrogen - - - - - - - - 6
25 An atom of carbonic oxide composed of 1 of carbone and 1 of oxygen - - - - - - - - 12
26. An atom of nitrous oxide, 2 azote + 1 oxygen - 17
27. An atom of nitric acid, 1 azote + 2 oxygen - - 19
28. An atom of carbonic acid, 1 carbone + 2 oxygen 19
29. An atom of carburetted hydrogen, 1 carbone + 2 hydrogen - - - - - - - - - - - - - 7
30. An atom of oxynitric acid, 1 azote + 3 oxygen 26
31. An atom of sulphuric acid, 1 sulphur + 3 oxygen 34
32. An atom of sulphuretted hydrogen, 1 sulphur + 3 hydrogen - - - - - - - - - - - - - 16
33. An atom of alcohol, 3 carbone + 1 hydrogen - 16
34. An atom of nitrous acid, 1 nitric acid + 1 nitrous gas - - - - - - - - - - - - - - 31
35. An atom of acetous acid, 2 carbone + 2 water - 26
36. An atom of nitrate of ammonia, 1 nitric acid + 1 ammonia + 1 water - - - - - - - - - 33
37. An atom of sugar, 1 alcohol + 1 carbonic acid - 35

J. Dalton *A New System of Chemical Philosophy, Part 1*, Manchester: S. Russell for Bickerstaff, Strand, London, 1808; Plate 4, p. 219.

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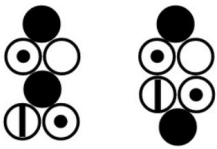
The prevailing model for understanding why different substances have different observable properties (state, color, taste, feel) was based upon elemental composition. As the first generation of substances was analyzed, every substance that was different from every other also exhibited a different elemental composition. In 1800, we would have said that a given substance with an elemental composition, by weight, of 48.98% carbon, 48.98% oxygen, 2.04% hydrogen is unique to that substance and no other. In modern terms, we might say that this particular collection of atoms ($C_4H_2O_3$) is unique to the substance undergoing analysis. This formula would be the same for any sample of that substance, and nothing else would provide the same analysis. Elemental composition, in other words, was thought to be the basis of chemical identity of a substance in the early 1800s. Molecules of a substance were thought of as an amorphous bag of atoms.

By 1811, there is direct evidence that Dalton was thinking about how certain groupings of atoms were recurring in different substances, and that the same set of atoms might be arranged differently and give rise to different substances. In 1915, 150 unpublished, handwritten sheets of diagrams that Dalton used as displays during lectures were discovered in an old cabinet at the Manchester Literary and Historical Society (Manchester, UK). The diagrams were correlated with dated notebook entries.

> Dalton attempted to represent the constitution of many organic compounds; a fact which would not be suspected from his published work. In many of these formulas for organic compounds he placed the atoms C H O in proximity: the note-books show that in 1811 he had the idea of an important part played by this group, which he called the "vegetable atom"...
>
> "vegetable atom"
>
>
>
> ... [the "vegetable atom" grouping appears as a part of two drawings, which]... shows the atoms C2, H2, O, N arranged in two different ways to represent albumen and gelatin [two completely different substances that, according to Dalton's reference, had the same elemental composition]:
>
> 
>
> albumin gelatin
>
> H.F. Coward A. Harden, *Memoires of the Manchester Literary and Historical Society, Memoire 12*, **1915**, (59), 41; and H.F. Coward, *Journal of Chemical Education*, **1927**, *4*, 23.

Although we only have this pair of drawings, and not his notes, Dalton was proposing to solve a significant mystery. Two different substances (in this case, albumen and gelatin) might indeed be composed of the same atoms (C_2H_2NO) if those atoms were arranged differently.

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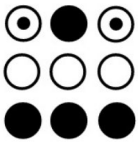
C. The Need for Molecular Structure and the Invention of Isomerism

The need to modify a scientific principle occurs when the existing principle(s) can no longer explain the observations.

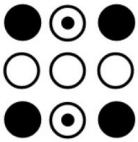
Basing the chemical identity of a substance on its elemental composition needed to be modified exactly when you think it might: to solve the problem of when two or more substance with wildly different properties ended up sharing the same elemental composition. Presumably, the first conclusion was that the elemental analysis experiments had been done incorrectly! But eventually, the results were repeated and carefully affirmed: two different substances can have the same elemental composition.

At this point in history, humans invented the idea of molecular structure to resolve this problem. The molecules of a substance could no longer be an amorphous bag of atoms. Instead, as Thomas Thomson wrote near the end of his famous 1830 book on the history of chemistry (pp. 303–305):

> There are two acids, the acetic and succinic, that are composed of exactly the same number, and the same kind of atoms…so that they consist of nine atoms.* Now as these two acids are composed of the same kind of atoms, one would expect that their properties should be the same; but this is not the case: acetic acid has a strong and aromatic smell, succinic has no smell whatsoever. Acetic acid is so soluble in water that it is difficult to obtain it in crystals, and it cannot be procured in a separate state free from water…; but succinic acid is not only easily obtained free from water, but it is not even very soluble in that liquid. The nature of the two salts formed by these two acids is quite different; the action of heat open each is quite different; the specific gravity of each differs. In short all of their properties exhibit a striking contrast. Now how are we to account for this?… As a substance then, containing nine atoms, such as acetic acid, must be of a very complex nature. … Thus, if we make use of Mr. Dalton's symbols to represent the atoms of hydrogen, carbon and oxygen we may suppose the nine atoms constituting acetic and succinic acid to be arranged thus:



Or thus:



> Now, undoubtedly these two arrangements would produce a great change in the nature of the compound.

Author's Note: As it turns out, acetic acid and succinic acid do have different numbers of atoms (acetic: $C_2H_4O_2$ and succinic: $C_4H_6O_4$), but the analyses available to the scientists in the early 1800s were not discriminating enough to distinguish between them. Thomson's point is both legitimate and significant.

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In modern terms, Thomson is describing how the same set of atoms can be organized into different molecular structures.

Acetic and succinic acids are derived from the vegetable or animal kingdom (from living systems, "organic" meaning "from organisms"). Minerals, which are not from living systems, were considered to be wholly different from organic substances ("inorganic" for "not organic"). In the 1830 textbook, Thompson is describing two organic molecules, acetic and succinic acids, which, at the time, were measured as having the same elemental composition. The phenomenon was not limited to organic substances. In 1827, Friedrich Wöhler demonstrated that two quite different inorganic substances (silver fulminate and silver cyanate) had the same elemental composition.

"Organic" and "inorganic" were important distinctions. In 1815, in trying to explain why organic substances were only found in living things, people believed that organic substances were imbued with a "vital force" associated with living things, and that (a) humans cannot prepare organic compounds from inorganic ones, (b) preparing organic compounds requires a vital force, and (c) the vital force is set by Divinity, so studying these compounds is not practical because they cannot be prepared. A year after his 1827 report, however, Wöhler also reported that the organic compound urea (found in urine) had the same elemental composition as the inorganic mineral, ammonium cyanate. Wöhler wrote:

> "This investigation has yielded an unanticipated result that reaction of cyanic acid with ammonia gives urea, a noteworthy result in as much as it provides an example of the artificial production of an organic, indeed a so-called animal, substance from inorganic substances."
>
> "In a manner of speaking, I can no longer hold my chemical water. I must tell you that I can make urea without the use of kidneys of any animal, be it man or dog. Ammonium cyanate is urea."

Wöhler's experiments are considered historically important for overturning the vital force theory and opening the door to the extensive study of organic (historically called "animal") chemistry.

Observations that different substances could have the same elemental composition proliferated, and the Swedish chemist Jöns Jacob Berzelius, in 1830, invented a new word to describe this new concept: isomer (iso- meaning "same" and –mer meaning "parts").

Constitutional isomers are different substances that have the same elemental composition. The corresponding property is called isomerism.

D. Models for Chemical Affinity and Bonding

The story of how humans developed the concept of molecular structure from the observation of isomerism is an excellent lesson about the process of science. Molecular structure was proposed to solve the problem of how the same set of atoms can result in substances with different properties.

The relationship between properties and molecular structure is the story of modern chemistry over the last 200 years, the core features of which were developed between about 1850–1950. These core ideas form the basis for the introduction to organic chemistry, and so the course is often subtitled as an introduction to structure and reactivity (property) relationship.

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Isomerism and molecular structure contributed to one of the greatest unanswered questions about chemistry in the early 1800s, and one that would not be answered for over 100 years: what was the force that was holding atoms together, and how does that force contribute to the ability to achieve these different fixed arrangements? From Democritus and Dalton, a physical model was used (hooks and eyes). In the post-Newtonian world, the placeholder terms for forces called "affinity" (meaning "attraction") and "chemical affinity" had been around for many years. This is typical of science: humans knew there was something that caused attraction, but did not know what it was, and so the property (attraction) was given a name that was a descriptive synonym ("affinity").

In the early 1800s, after Alessandro Volta created the first batteries (voltaic piles), chemists carried out experiments where electricity could cause the decomposition of substances into their elements (notably the electrolysis of water into hydrogen and oxygen gases). The association between electricity, which was itself not understood, and the "chemical affinity" of atoms was clear, and the quite familiar terms electropositive, electronegative, cation (ion, a moving particle, that goes to the cathode), and anion (an ion that goes to the anode) all derive from these experiments (Figure 0104) on next page.

Subatomic particles were not discovered for about a hundred years after the electrolysis experiments (electrons, 1896; protons, 1920; neutrons, 1934), and Gilbert Lewis's model of the 2-electron chemical bond, dating from 1916, forms the foundation of our modern ideas about chemical affinity. Your prior studies of chemistry are built upon the understanding of atoms, molecules, and the periodic table that result from the model using these subatomic particles.

Before moving into the details of organic molecular structure and reactions, which begins in the next section, you now have a little work to do.

Some prior knowledge about general chemical principles is assumed when studying organic chemistry. It is not too much, but it is critically important. Every student's experience with high school and/or college-level General Chemistry is different, and everyone forgets (or perhaps misunderstood) a different aspect of the subject. Or, equally so, your background may be fine, and you can proceed, full speed ahead.

As an organic chemistry textbook, we are not going to revisit those prerequisites in their complete detail, as though you were learning them for the first time. Instead, you can find a brief overview of some of the most significant topics expected from a study of General Chemistry in Appendix 1 (Useful Expectations from General Chemistry). Do not ignore these materials! Take this opportunity to revisit the ideas of atoms, ions, and molecules, the periodic table and its trends, and some of the explanatory models for phenomena such as dissolving and evaporation.

This first set of practice problems is unique in that they follow from the Appendix. These questions have been designed to emphasize the prior knowledge that is expected from an introduction to chemistry before you take an organic chemistry course. Your instructor might also spend a few moments on some of these topics, too, in an effort to give everyone a sense of these expectations from your prior study of chemistry.

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Figure 0104

Are you positive about why you are positive?

Electrolysis of water and the historical terms associated with it.

1747: Assigning Signs

Benjamin Franklin assigns "+" and "-" to throwing off or drawing in the electrical fire.

⊕ ⊖

In a May 25, 1747, letter to Peter Collison, Franklin describes the current thinking about electricity (the "electrical fire") as having opposite types that enable the explanation for the observation of attraction and repulsion of electrified objects. Sometimes the electrical fire is built up (has an over-quantity relative to the surroundings) and is "electrised positively" or "plus" with a repulsion of the electrical fire (a high pressure of the electrical fluid); while a deficiency of the electrical fire means it is "electrised negatively" or "minus" with an attraction of the electrical fire (a low pressure area).

1830: Elemental Charges

Thomas Thomson teaches the world about chemistry.

⊕ O^- electro-negative

⊖ H^+ electro-positive

Thomson was fortunate enough to be creative, insightful, and a prolific writer of great clarity. He advanced chemistry in the late 1700s by introducing the first system of using symbols. More importantly, through conversations he recounts in his 1830 *History of Chemistry*, he was completely sold on Dalton's view of atomism and nearly singlehandedly popularized it in the 1807 (third edition) of his "System of Chemistry." More than a mere reporter, Thomson took the ideas he encountered and ran with them. Fifty years after Franklin introduced "+" and "-" into the world, the first voltaic piles (batteries) were being made and, in addition to making frog legs twitch, the effects of electricity to be able to decompose chemical substances became the first comprehensive theory for what had been called chemical affinity (the reason for atoms to cling together).

Recounting experiments by Davy and others from 1800–1803, Thomson (1830) writes: "Thus it was demonstrated that water was decomposed by the action of the pile and that the oxygen was extracted from the positive pile and the hydrogen from the negative." Atoms were seen as being coated by either the positive or negative form of electricity, and so oxygen and others were assigned as being "electro-negative" for their observed appearance at the previously labeled positive pole; whereas hydrogen and others were assigned to be "electro-positive."

1834: Using New Words

Michael Faraday creates explanations with mobile atoms and needs some new words.

⊖ ⇦ H^+ O^- ⇨ ⊕

The electrolysis (to analyze or break down with electricity) of water is representative of the broader observation of electrical decomposition and contains the inference about the electrochemical nature of chemical affinity. Faraday needs new words to convey his ideas about how and why the "electro-negative" (i.e., electrically deficient in the Franklin sense) oxygen atoms move from being part of water and picking up (in 1834 thinking) some current, to become oxygen gas.

For Faraday, the "determining force" does not lie in the battery, but within the body that is decomposing, with the battery being a conduit. The need to tell the story and for language to be useful is a keen lesson in science.

Faraday (1834) writes: "To avoid confusion, and for the sake of greater precision of expression than I can otherwise obtain, I have deliberately considered the subject with two friends, and with their assistance and concurrence in framing them, I purpose henceforth using certain other terms, which I will now define."

1834: Building New Words

William Whewell invents the words Faraday needs.

anode cation anion cathode

⊖ ⇦ H^+ O^- ⇨ ⊕

In an emerging age of specialization, Whewell was one of the last great polymaths, publishing contributions in areas of mathematics, poetry, economics, theology, physics, astronomy, and geology. But by far, we owe Whewell thanks for his mastery of language. A noted wordsmith, he consulted with many colleagues to work through ideas of what to call something. Among others, he is credited with coining the terms scientist, physicist, and linguistics.

Faraday consulted with Whewell (and gives credit) for the terms introduced in 1834 related to the electrical decomposition of substances, and they are probably more important in chemistry today than they were then.

Rather than using the term "pole" for positive and negative ends of the voltaic pile, the term "electrode" was created to represent the place where current entered and left from the decomposing material (whereas the earlier notion of the pole was the place where positive and negative electrical density were being built up for discharge). Faraday wanted to establish a convention of representing the current traversing the decomposing body from "East to West" (as in the apparent motion of the sun) so the East is where the current enters the decomposing body (the positive electrode, the way up; where electricity is built up) and exits the decomposing body in the West (the negative electrode, the way down; where the decomposing body deposits its electricity). Hence, the positive electrode was called the anode (the "an" representing the way up, same as its use in biology as anabolism), and the negative electrode was called the cathode, signifying "descent" or "the way down" (as in catabolism). The individual atoms, charged as they were either electro-negative or electro-positive, r complementary electrode. The collective term for these moving particles was , the electro-negative ion moved to the (positive) anode and was to be called an e (negative) cathode, was to be called a "cation."

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D. Models for Chemical Affinit...
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PRACTICE QUESTIONS

1.01 Using Lewis structures, provide accurate representations for the following atomic and molecular species. Nonbonding electron pairs should be shown as dots, shared electron pairs should be shown as lines, formal charges should be indicated, and the valence electrons for uncharged metals should not be shown. Ionic compounds should be shown as separated ions.

(a) bromide ion | bromine atom

(b) chlorine molecule | nitrogen molecule

(c) ammonia molecule | ammonium ion

(d) water molecule | hydronium ion

(e) sodium cation | sodium atom

(f) hydrogen molecule | hydrogen atom anion

1.02 Place a small "X" in any of the 12 boxes, above, in the answers for question 1.01, where there are atom(s) that have an open shell electron configuration.

1.03 Using Lewis structures, provide accurate representations for the following atomic and molecular species. Nonbonding electron pairs should be shown as dots, shared electron pairs should be shown as lines, formal charges should be indicated, and the valence electrons for uncharged metals should not be shown. Ionic compounds should be shown as separated ions.

(a) hydrogen iodide | nitrogen triiodide

(b) ammoniun fluoride | potassium fluoride

(c) lithium metal | lithium chloride

(d) magnesium dichloride | carbon tetrachloride

(e) sodium hydroxide | ammonium hydroxide

(f) hydrogen bromide | hydronium bromide

1.04 In your answers to questions 1.01 and 1.03, identify all of the polar covalent bonds and place the symbols for partial positive (δ^+) and partial negative (δ^-) charges on the appropriate atoms.

1.05 Dibromine monooxide is a triatomic molecule with all closed shell atoms and no formal charges on any of the atoms. Draw dibromine monooxide.

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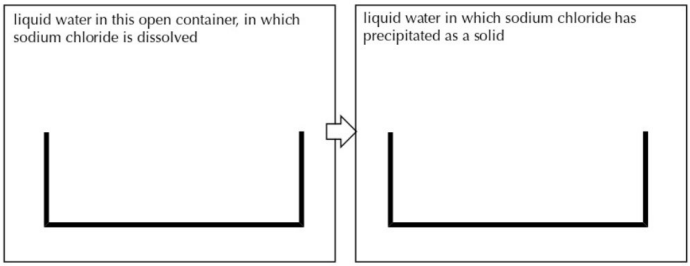
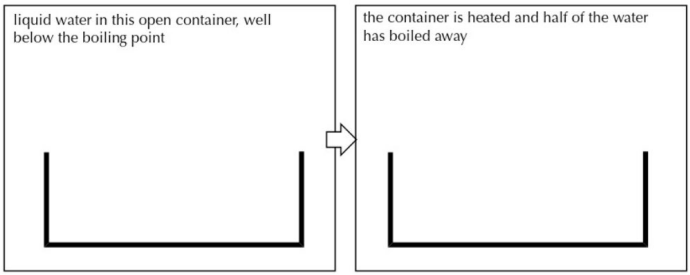
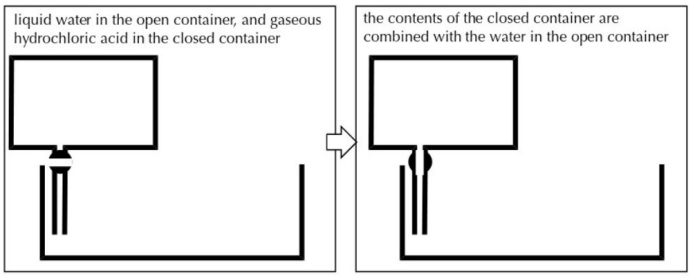
1.06 Before and After: In each of the two spaces below, using 15 water molecules and the ions from 4 molecules of sodium chloride, show the following:


liquid water in this open container, in which sodium chloride is dissolved
liquid water in which sodium chloride has precipitated as a solid

1.07 Before and After: In each of the two spaces below, using 15 water molecules, show the following:


liquid water in this open container, well below the boiling point
the container is heated and half of the water has boiled away

1.08 Before and After: In each of the two spaces below, using 15 water molecules and 5 molecules of hydrogen chloride (hydrochloric acid, a gas), show the following:


liquid water in the open container, and gaseous hydrochloric acid in the closed container
the contents of the closed container are combined with the water in the open container

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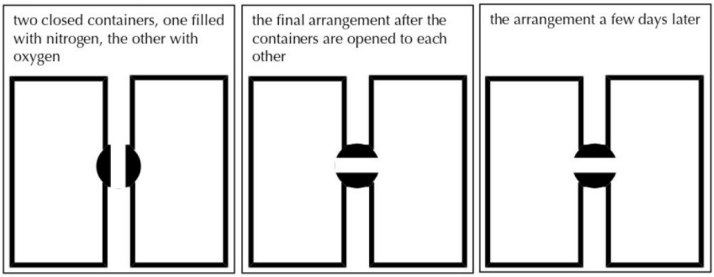
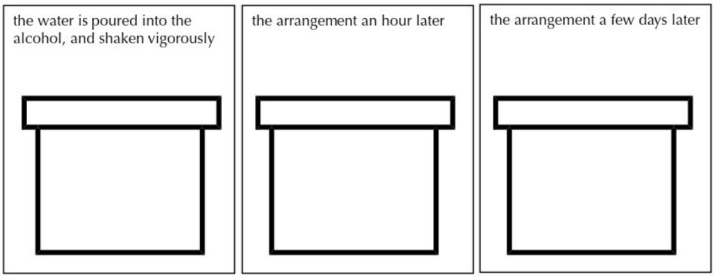
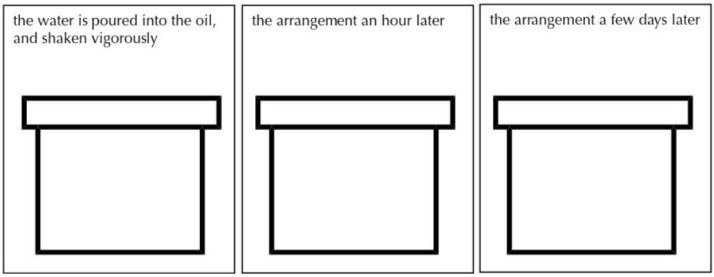
1.09 Before and After: In each of the three spaces below, using 15 nitrogen "N_2" molecules and 15 oxygen "O_2" molecules, show the following:


two closed containers, one filled with nitrogen, the other with oxygen
the final arrangement after the containers are opened to each other
the arrangement a few days later

1.10 Before and After: In each of the three spaces below, in the lidded container, using 15 water "W" molecules and 15 alcohol "A" molecules (W is more dense that A, and they are miscible), show the following:


the water is poured into the alcohol, and shaken vigorously
the arrangement an hour later
the arrangement a few days later

1.11 Before and After: In each of the three spaces below, in the lidded container, using 15 water "W" molecules and 15 oil "O" molecules (W is more dense that O, and they are immiscible), show the following:



1.12 You are expected to have encountered the phenomena in questions 1.09-1.11 in real life. What are the explanations for each of the outcomes you have illustrated?

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1.2 Three Principles About Chemical Reactions

A. Atoms Are Conserved in Chemical Reactions

The most familiar principle about chemical reactions is that the number and kind of atoms are conserved (meaning, stay the same) from the start (starting materials, reactants) to the end results (products and by-products). Historically, this conservation principle was based on weight measurements, accounting for the mass of all of the starting materials showing up in the products. The development of the atomic and elemental theories meant that we started talking about keeping track of the atoms, and that they were neither created nor destroyed, during reactions.

In the early 1800s, chemists invented the word stoichiometry (in English, 1807, from a German term; Stöchiometrie, 1792) to represent the process of keeping inventory of weights, and then atoms. The word means "a measurement of elements (as in a list or inventory)." In introductory chemistry, you learn about balancing chemical equations, and also about how much mass might be needed for, or formed in, a reaction. These procedures all fall under the heading of stoichiometry calculations (see Figure 0105 for some representative balanced equations).

Figure 0105
Some balanced equations (elemental composition only).

i) $C_3H_4 + 2\,Br_2 \longrightarrow C_3H_4Br_4$

ii) $C_5H_{10} + H_2 \xrightarrow[\text{catalyst}]{\text{metal}} C_5H_{12}$

iii) $C_6H_{11}Cl + NaOH \longrightarrow C_6H_{10} + H_2O + NaCl$

iv) $C_6H_{10}O_2 \xrightarrow[\text{catalyst}]{\text{acid}} C_6H_6 + 2\,H_2O$

v) $C_5H_{12}O + HCl \longrightarrow C_5H_{11}Cl + H_2O$

vi) $C_{10}H_{10} \xrightarrow[\text{catalyst}]{\text{metal}} C_{10}H_8 + H_2$

vii) $C_5H_8O_2 \xrightarrow{NaH} NaC_5H_7O_2 + H_2$
$C_5H_8O_2 \xrightarrow{2\,NaH} Na_2C_5H_6O_2 + 2\,H_2$

viii) $C_{12}H_{20} \xrightarrow[2)\,3\,Zn]{1)\,3\,O_3} C_3H_6O + C_7H_{10}O_3 + 2\,CH_2O + 3\,ZnO$

The stoichiometric ratio between different chemical substances, derived from the coefficients in the balanced equation, is often expressed linguistically as the number of "molar equivalents" (or simply "equivalents"). These relationships are used to express a few different things: (a) the ratio or amounts of substances that are needed for a reaction according to the stoichiometric ratio in the balanced equation, (b) the ratio of reactants used under the experimental conditions, which might be different from the stoichiometric ratio in the balanced equation (if an excess or restrictive limit was desired), and (c) the prediction of what is needed and/or what is missing can be identified to balance the equation. Features of the balanced equations are also used to characterize or classify reactions (for instance, a molecule that loses water is said to have undergone a "dehydration reaction"). Examples of the use of stoichiometric language, including explanations and some classifications, can be found in Figure 0106.

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a) $C_3H_4 + 2\ Br_2 \longrightarrow C_3H_4Br_4$

- there is a 1:2 stoichiometric ratio between C_3H_4 and Br_2
- C_3H_4 reacts with 2 equivalents of Br_2 to give $C_3H_4Br_4$
- the transformation of C_3H_4 to $C_3H_4Br_4$ is called a bromination reaction
- if greater than 2 equivalents of Br_2 was used, you may not assume that no additional reaction would occur (that information is not provided)
- by analogy, it would be expected that C_3H_4 would react with 2 equivalents of Cl_2 to give $C_3H_4Cl_4$

Figure 0106
Restatements, interpretations, and inferences from chemical equations.

b) $C_5H_{10} + H_2 \xrightarrow[\text{catalyst}]{\text{metal}} C_5H_{12}$

- there is a 1:1 stoichiometric ratio between C_5H_{10} and H_2
- C_5H_{10} reacts with 1 equivalent of H_2 to give C_5H_{12}
- the transformation of C_5H_{10} to C_5H_{12} is called a hydrogenation reaction
- if greater than 1 equivalent of H_2 was used, you may not assume that no additional reaction would occur (that information is not provided)
- some reactions required catalysts (this information is simply provided for now)

c) $C_6H_{10}O_2 \xrightarrow[\text{catalyst}]{\text{acid}\ \ or\ \ \text{dehydratase enzyme}} C_6H_6 + 2\ H_2O$

- 2 equivalents of water form from each $C_6H_{10}O_2$
- the transformation of $C_6H_{10}O_2$ to C_6H_6 is called a dehydration reaction
- biological catalysts (enzymes) that cause dehydration reactions are called dehydrases (older term) or dehydratases (newer term)
- some reactions required catalysts (this information is simply provided for now)

d) $C_{10}H_{10} \xrightarrow[\text{catalyst}]{\text{metal}} C_{10}H_8 + H_2$

- 1 equivalent of hydrogen forms from each $C_{10}H_{10}$
- the transformation of $C_{10}H_{10}$ to $C_{10}H_8$ is called a dehydrogenation reaction
- biological catalysts (enzymes) that cause dehydrogenation reactions are called dehydrogenases (older term) or oxidases (newer term)
- some reactions required catalysts (this information is simply provided for now)

B. Main Group Elements Have Simple and Reliable Bonding Patterns

On the periodic table, the elements in groups 1 and 2 (the hydrogen/lithium and beryllium columns, or s-block elements) and groups 13–18 (the boron to helium/neon columns, or p-block elements) have quite consistent oxidation states and bonding patterns. These groups are called the main group elements, in contrast with the transition elements in the center of the periodic table. The valence and bonding patterns for the main group elements are particularly reliable for its lightest members, in the first and second rows, where closed shell electron configurations of 2 (duet rule: hydrogen, helium, and the lithium and beryllium cations) and 8 (octet rule: boron through neon) are not predicted to be exceeded without direct evidence. There are often exceptional cases, but it is reasonable to expect that experimental information will be provided.

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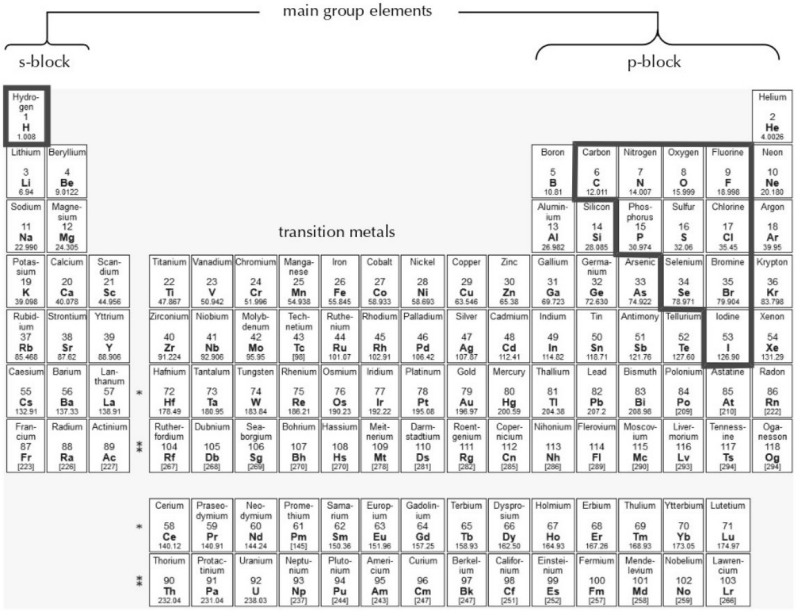
Organic compounds in nature are primarily made up of carbon, hydrogen, nitrogen, oxygen, phosphorus, sulfur, rarely selenium, and the halogen atoms (mainly chlorine and bromine, and then iodine, and rarely fluorine). Which is not to say that other elements are not important for sustaining life. Metal ions are also absolutely critical to biological function (e.g., the iron ions in hemoglobin that carry oxygen molecules). The bonding in this subset of organic main group elements (Figure 0107) is extremely consistent and predictable because of the dominant role that achieving a closed shell electron configuration plays in chemistry.

Figure 0107
Periodic table.



Periodic table indicating the main group elements, transition metals, and most common organic main group elements (bold outline).

Although models for bonding based on electrons were not invented until subatomic particles were discovered in the early 20th century, the regular bonding patterns of these organic main group elements were observed in the early 19th century. Over and over again, carbon was observed to combine with a value of 4 (4 bonds, either to other atoms or with itself for some of them), nitrogen combined with a value of 3, oxygen with 2, and hydrogen and the halogens with 1. In 1884, the "combining power" or "value" of an atom was called its valence (from the German, *valenz*).

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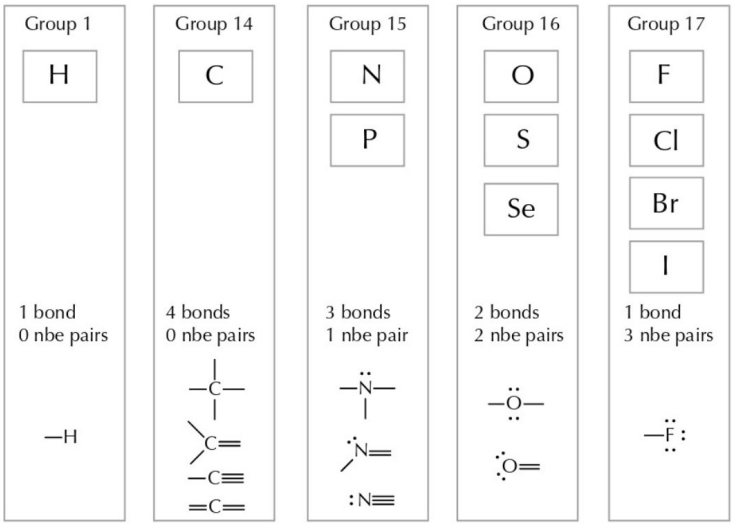
In the 20th century, the model for atoms and their bonding that included protons, neutrons, and electrons further clarified the reasons for these valences. Alone, as on the periodic table, atoms have a net charge of zero because the number of protons equals the number of electrons. When atoms share electrons in covalent bonds, to achieve a closed shell electron configuration, they are neither giving up nor taking on or losing any net electrons, so the charge of zero does not change. The vast majority of atoms, consistent over thousands of different examples you will encounter in organic molecules, will exhibit the bonding patterns of uncharged atoms with closed shell electron configurations.

The bonding pattern (number of bonds and nonbonding electron [nbe] pairs generalizations for the closed shell, uncharged atoms of the organic main group elements are provided in Figure 0108.

Figure 0108

Uncharged, closed shell generalizations for organic main group elements.



For any given molecular formula, there are usually many rational organic molecular structures where all of the atoms are observed to have these closed shell, uncharged atoms. Generating the complete set of options by hand requires some trial and error, some experience, and once the number of atoms starts to grow, more or less requires a computer program to be sure that all of the possibilities are accounted for. It is a useful exercise to try generating these various options, which would all be considered the structural (constitutional) isomers of the given molecular formula. However, this exercise is not a good quiz or exam question unless someone tells you just how many possible structures there are in the first place, because there is no simple calculation for knowing when you have a complete set.

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B. Main Group Elements Have Si...
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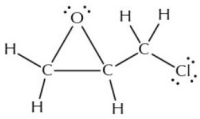
In Figure 0109, a few examples of structural (constitutional) isomers for some molecular formulas are provided. Note that all of the atoms adhere to the uncharged, closed shell generalizations. Note also that, as Thomas Thomson described in his 1830 textbook, molecules with the same molecular formula can indeed have quite different properties based on their structures.

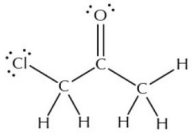
Figure 0109
Examples of structural isomerism.

molecular formula: C_3H_5ClO



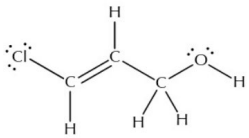
epichlorohydrin

a building block for epoxy resins and a cancer suspect agent



chloroacetone

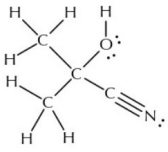
a lachrymator used in a gas weapon during WWI



3-chloroallyl alcohol

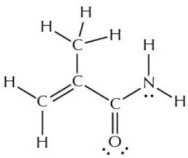
a pollutant residue found after using a common pesticide

molecular formula: C_4H_7NO



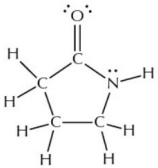
acetone cyanohydrin

highly toxic source of hydrocyanic acid (HCN) when exposed to water



methacrylamide

used to form the cement used to bond bone replacements to bone



2-pyrrolidone

used in inkjet cartridges

Examples of structural isomerism using organic main group elements, all of which have atoms that are uncharged and have closed shell electron configurations.

The particular bonding arrangement of atoms in a given molecule (which ones are connected to what others) is called the connectivity of the structure. Different structural isomers have different connectivity. Spatial and geometrical considerations do not play a role in defining connectivity, as it only refers to the map of the atoms. Similarly, the occurrence of single versus multiple bonds does not matter to defining connectivity. Quite simply, connectivity, just as the name implies, is a description of which atoms are bonded to one another.

The structures in Figure 0110 are all examples of different molecules with different connectivity that share the same molecular formula. One skill to develop in learning organic chemistry is how to recognize that two quite different-looking drawings can be representations for the exact same molecular structure. In Figure 0110, a few drawings that represent both the same and different connectivity for structures in Figure 0109 are compared.

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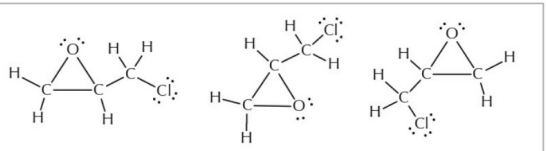
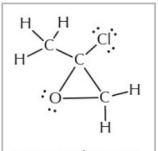
Figure 0110
Connectivities.

molecular formula: C_3H_5ClO

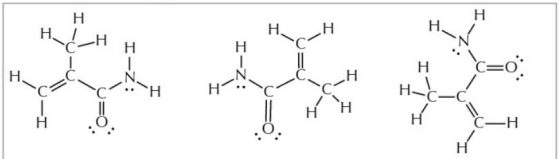


all 3 of these drawings have the same epichlorohydrin connectivity

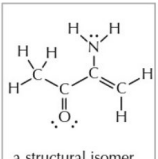


a structural isomer of epichlorohydrin

molecular formula: C_4H_7NO



all 3 of these drawings have the same methacrylamide connectivity

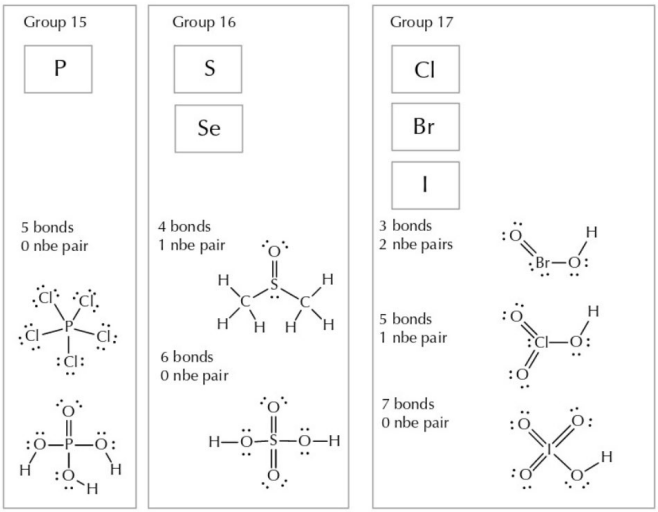


a structural isomer of methacrylamide

Examples of drawings that represent the same and different connectivities.

Elements in the third (and lower) rows, can sometimes show bonding patterns that go beyond the generalizations seen for the first and second row elements. These bonding patterns are quite commonly observed when the elements are combined with oxygen and halogen atoms, and they are called hypervalent (sometimes "expanded octet") structures. A few familiar, representative examples of hypervalent structures are in Figure 0111.

Figure 0111
Examples of molecules with hypervalent atoms from groups 15–16.



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C. Chemical Reactions Are Subtle Bonding Changes and Rarely Explosions

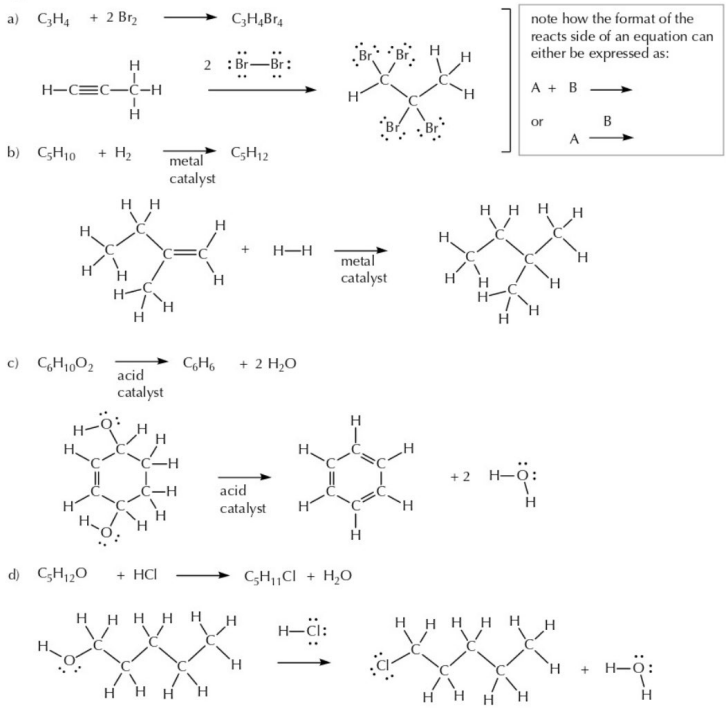
The bonding in organic molecules is relatively strong and stable. The biological function of organisms relies on most parts of a molecular structure not changing its connectivity too easily. On the other hand, organic chemical reactions are defined by the change in connectivity that takes place, so many organic reactions are characterized by a few bonding changes that take place against a sturdy framework of atoms.

In organic chemical reactions, it is exceedingly rare for molecules to completely fly apart into their constituent atoms and then have the atoms reassemble into a completely new molecule or set of molecules. In general, you should expect individual reactions to be about 1-4 changes in the connectivity of the atoms, where 1-2 bonds break and 1-2 bonds form. And other than that, the connectivity of the molecule is maintained during the reaction. From a practical standpoint, that means that you end up recopying much of the structure when you show an organic chemical reaction.

In Figure 0112, some of the balanced equations from Section 1.2 (Figure 0106) are exemplified with one set of structures that could represent the chemical reaction. These particular examples are in no way

Figure 0112

Examples of some observed bonding changes.



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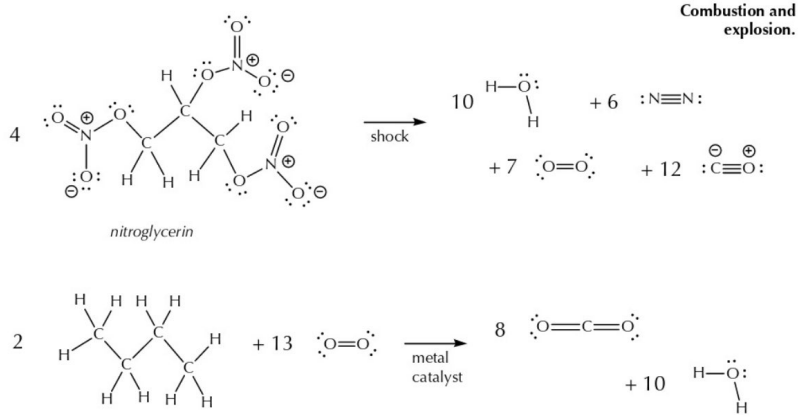
implied by the molecular formulas, and there are many other examples that could illustrate the point equally well. You are not yet expected to understand how or why these changes take place, but you should note that, in these examples, all of the atoms maintain the uncharged, closed shell generalizations on both sides of the equation.

As implied by the title of this section, explosions are not subtle changes. Explosives can be organic molecules that can decompose rapidly, releasing heat energy, and form a large collection of small molecules. The compressed volume of hot gaseous molecules expands rapidly as a shock wave. The reaction of explosive molecules is fast and does not require the mixing with oxygen, as combustion does. Not as dramatic as an explosion, burning organic molecules in a normal atmosphere (combustion) is also a case where the original connectivity can be completely lost. Combustion can be hotter and/or more explosive when the fuel (the organic molecules) is premixed with oxygen before it is ignited because the reaction between these two components can occur more rapidly (Figure 0113).

Figure 0113
Combustion and explosion.



The balanced equations of nitroglycerin (an explosive) and the combustion reaction of butane (found in a disposable lighter).

D. The Logic of Chemical Reactions I

With enough information about a reaction, the three principles from this section combine to provide chemists with a powerfully useful model for deducing an unknown structure for chemical reactions.

Principle 1: Atoms Are Conserved in Chemical Reactions
Principle 2: Main Group Elements Have Simple and Reliable Bonding Patterns
Principle 3: Chemical Reactions Are Subtle Bonding Changes and Rarely Explosions

For example, chloroacetone, one of the C_3H_5ClO structural isomers from Figure 0109, is listed as a lachrymator, which means it causes your eyes to tear up. This chemical process happens when chloroacetone is exposed to water and releases hydrochloric acid (hydrogen chloride, H-Cl). The reaction with water to release hydrochloric acid is also why chloroacetone was used as a "poison gas" on the battlefields of World War I. When it is inhaled, the reaction with water can happen in the lungs, which causes an irritation that rapidly results in a massive amount of fluid buildup, suffocating the victim.

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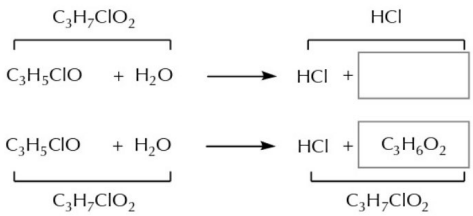
From the information in this passage, and using the three principles, you can provide an answer to the question: What is the chemical equation for the reaction of chloroacetone with water? The information can be rewritten as an equation with a missing piece. On the left-hand side of the equation (reactants), chloroacetone is reacting with water. On the right-hand side (products), hydrochloric acid is formed.

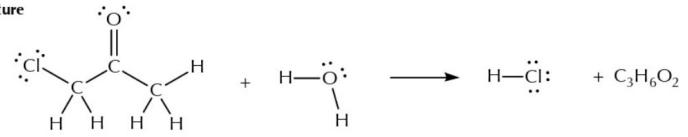
The text of the previous paragraph can be rewritten as an equation. Because atoms are conserved (Principle 1), the equation is incomplete, but can be completed (Figure 0114):

Figure 0114
Completing a balanced equation.



Using the molecular structure for chloroacetone provided earlier, the equation can be represented more explicitly for this example (Figure 0115).

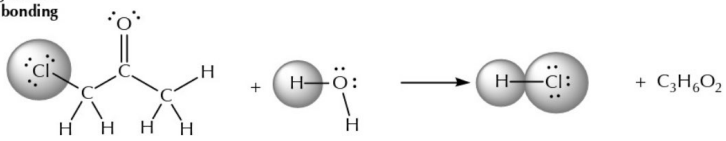
Figure 0115
Adding organic molecular structure to a balanced equation.



chloroacetone

Before applying the third principle, a conclusion must be drawn about where the "H" and the "Cl" came from to form the HCl product. Specifically, while the "Cl" atom must have come from the chloroacetone (the only place where there is a chlorine atom), the "H" in H-Cl needs to have come from the water. The logic for the "H" coming from the water molecule comes from two pieces of evidence: (a) the observation states that water is required for the reaction, and (b) the oxygen is incorporated into the "C3H6O" product, and the only way for the oxygen atom to be bonded in that molecule is to have relinquished one of its O-H bonds in the water molecule. Thus, the conclusion is that for the "Cl" to form, the HCl has to come from the chloroacetone and the "H" has to come from the water (Figure 0116).

Figure 0116
Accounting for the atoms in a bonding change.



chloroacetone

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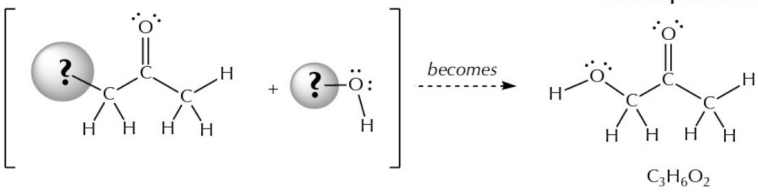
Based on the principle of reactions being simple changes (Principle 3), then, only the carbon-chlorine bond needs to have been broken in the chloroacetone to make the chlorine atom available, and only one of the hydrogen-oxygen bonds of water needs to have been broken to make the hydrogen atom available.

The HCl molecule is consistent with the uncharged, closed shell atom generalization (Principle 2). The carbon atom released when the carbon-chlorine bond is broken needs to be attached to a new atom to replace the chlorine. And the oxygen atom released when the hydrogen-oxygen bond is broken also needs a replacement for the hydrogen atom that was lost. The simplest remedy for these needs is to connect the oxygen to the carbon, which also fulfills the second principle (Figure 0117).

Figure 0117

Second and third pinciples applied to deduce a product's structure.

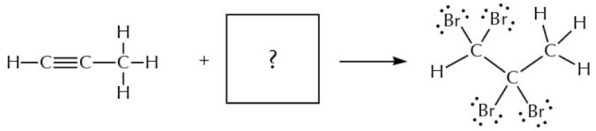


The resulting C_3H_6O molecule is the prediction for what results from chloroacetone when it reacts with water. Later in the course, the chemical basis for this change will be examined and explained. For now, this example illustrates exactly the type of experimental information one might obtain in the laboratory upon carrying out this reaction. The detailed explanation will always follow from an initial experimental observation.

Notice how, starting with any one of the complete equations in Figure 0112, removing one of the molecules from the equation creates new questions that can be answered by exactly the same application of the three principles comprising this lesson (Figure 0118).

Figure 0118

A new question based on an earlier example.



The importance of being able to use these three principles quite automatically cannot be underestimated in your study of organic chemistry. Looking at new structures and taking a fast and accurate inventory of (a) whether or not the structure is rational, and (b) whether or not and where the atoms have been accounted for, along with (c) assuming that a few simple changes have taken place and most of the molecules are still intact, adds considerably to your ability to learn organic chemistry.

In the next question set, as in some of the figures in this section, unfamiliar and unexpected experimental information such as the presence of catalysts or other reaction conditions are included. This information is included for scientific honesty, but it will not affect your ability to make predictions about reactions as you answer these questions.

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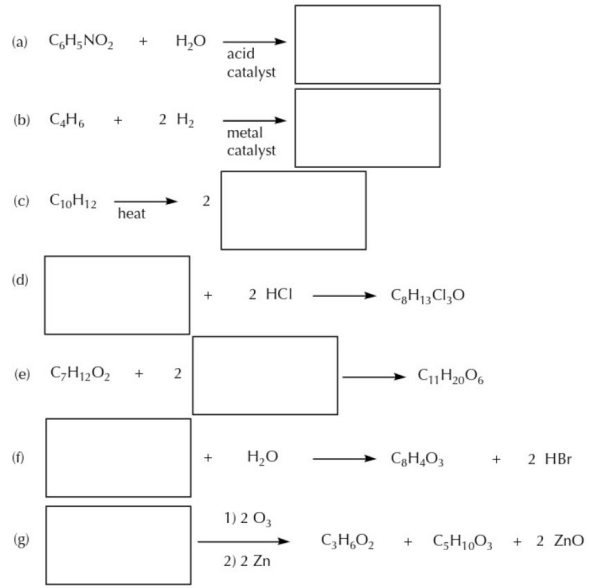
PRACTICE QUESTIONS

1.13 Provide the molecular formulas needed to balance the following chemical equations. In cases were the stoichiometric ratio is not 1:1, the corresponding coefficient is provided.


(a) $C_6H_5NO_2$ + H_2O → acid catalyst
(b) C_4H_6 + 2 H_2 → metal catalyst
(c) $C_{10}H_{12}$ → heat 2
(d) + 2 HCl → $C_8H_{13}Cl_3O$
(e) $C_7H_{12}O_2$ + 2 → $C_{11}H_{20}O_6$
(f) + H_2O → $C_8H_4O_3$ + 2 HBr
(g) 1) 2 O_3 2) 2 Zn → $C_3H_6O_2$ + $C_5H_{10}O_3$ + 2 ZnO

1.14 Rewrite the following statements as balanced chemical equations.

(a) When C_5H_8O and $C_4H_4O_2$ are heated together, they combine to give a single product in which they have reacted in a 1:1 stoichiometric ratio.

(b) $Li_2C_6H_8O_4$ plus 2 equivalents of another product are formed when $C_6H_{10}O_4$ reacts with 2 equivalents of LiOH.

(c) $C_9H_{18}O_3$ reacts with a dehydratase enzymatic catalyst (see Figure 0106) to give two products in a 1:1 stoichiometric ratio.

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1.15 Provide four structural isomers for each of the following molecular formulas. The atoms should all be uncharged and not hypervalent, and also have closed shell electron configurations. Nonbonding electron pairs should be included. If it is convenient, compare your replies with a classmate and decide (a) are all four of yours and theirs actually correct and different from one another (within your sets of four)? and (b) are there some that you have created that are the same? Please note that there are many different possible structures for these molecular formulas, and it is not an easy task to construct the complete set of isomers, so you need to rely on your assessment skills and conversations to evaluate the correctness of your replies.

(a) C_4H_7NO

(b) $C_5H_9Cl_3$

(c) C_4H_5BrO

1.16 When 1 equivalent of bromine (Br_2) reacts with C_4H_6, $C_4H_6Br_2$ is observed to be the exclusive product. If 2 equivalents of bromine are used, then $C_4H_6Br_4$ is observed and also forms exclusively. Based on these observations, what would be the result [molecular formula(s)] if 1.5 equivalents of bromine are used?

1:1 stoichiometric ratio

$$C_4H_6 + Br_2 \longrightarrow C_4H_6Br_2$$

exclusive
(i.e., no other products)

1:2 stoichiometric ratio

$$C_4H_6 + 2\ Br_2 \longrightarrow C_4H_6Br_4$$

exclusive
(i.e., no other products)

1:1.5 stoichiometric ratio

$$C_4H_6 + 1.5\ Br_2 \longrightarrow ?$$

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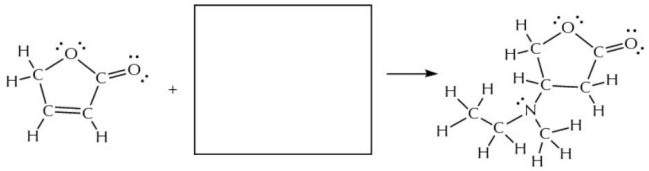
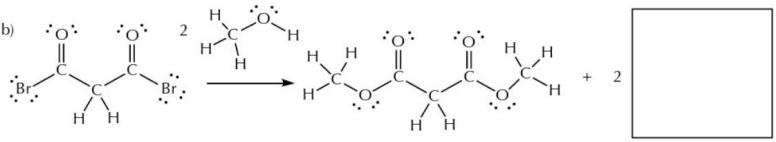
1.17 Provide the missing structures in the following chemical reactions by applying the three principles outlined earlier in this section: (1) atoms in chemical reactions are balanced, (b) the bonding patterns for organic main group elements are consistent and predictable, and (c) nearly all chemical reactions involve subtle rather than dramatic changes in bonding.

(a)



(b)



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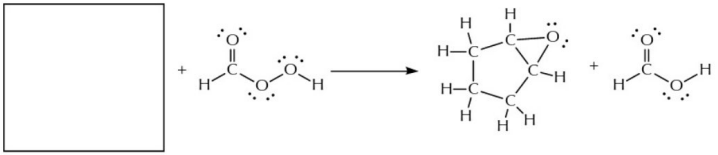

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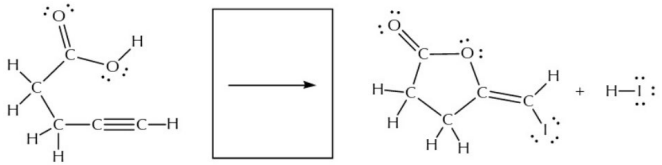
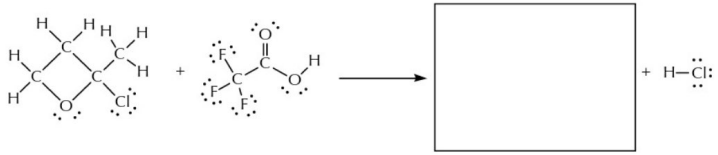


(e)



(f)

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1.3 Symbols and Their Meanings

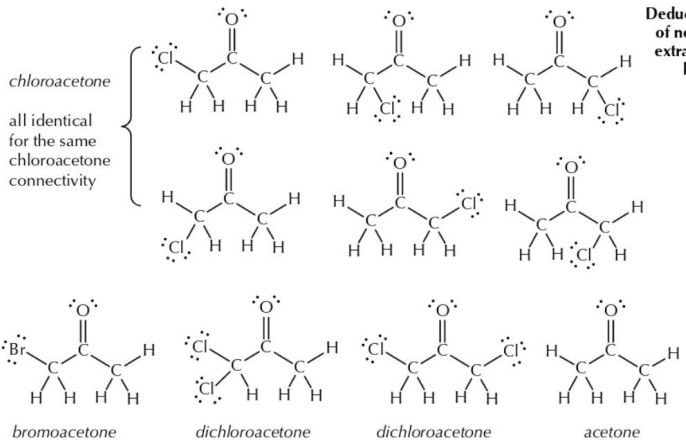
A. The Logic of Chemical Reactions II

The organic main group elements are a finite number of atoms that recur in organic molecules. According to the three principles laid out in the previous section, there are regular and predictable bonding patterns for the atoms within organic structures and in the chemical reactions of organic molecules. Another significant consequence of this predictable regularity is the ability to extrapolate and create analogies between structures and reactions that you have seen and those you have not (Figure 0119).

The "chloroacetone" examples presented in Figure 0119 are a good self-test for whether you understand what we mean by "connectivity." There is only one molecule with the chloroacetone connectivity: swapping the chlorine atom with any of the other hydrogen atoms in that structure creates a drawing with exactly the same connectivity. Connectivity, as the term implies, only relates to the connection map of the atoms, and not at all to any geometrical or spatial relationships. No matter which of these drawings you select, this is true: a chlorine atom is attached to a carbon with two hydrogen atoms, and that carbon is in turn attached to a carbon that is double bonded to an oxygen atom and one other carbon with three hydrogen atoms on it.

Starting with "chloroacetone" as the name for this connectivity, other related structures can be drawn and named by analogy. Using a bit of logic and your knowledge of the bonding properties of organic main group elements, along with a little imagination, structures can be proposed for (a) bromoacetone, (b) two different dichloroacetone isomers, and (c) acetone, itself, which lacks the chlorine atom.

Figure 0119
Deducing the identity of new structures by extrapolation from a known example.



Be sure you understand what this statement means in the context of viewing, understanding, and drawing molecular structures: there is only one molecule with the chloroacetone connectivity, one molecule with the bromoacetone connectivity, two and only two molecules with the dichloroacetone connectivity, and one molecule with the acetone connectivity.

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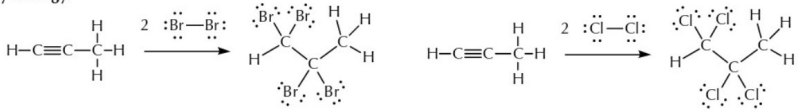
Making analogies when learning about organic chemical reactions is both common and practical. Once you have a good example to use, as well as some guidelines on its limitations, an observation can be used to make predictions for many different molecules. Looking again at an earlier example from Figure 0112, an organic molecule with a triple bond was shown to react with 2 equivalents of molecular bromine. This organic molecule can react with molecular chlorine in an analogous manner (Figure 0120).

Figure 0120

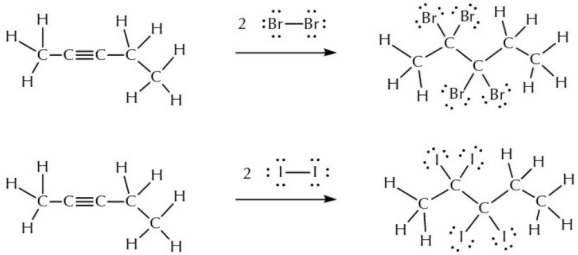
Understanding new reactions by analogy.



Even more powerfully, this reaction extends to many different organic molecules that have a triple bond, because this part of the molecule is its site of reactivity. This guidance about the reactivity of the triple bond means that thousands of different organic molecules with triple bonds can be expected to undergo an analogous change: that is, two of the bonds of the triple bond are broken, and four new bonds between those two carbons and the halogen atoms are formed (Figure 0121). As above, when you have the guideline that the reactions of molecular bromine and molecular chlorine also apply to the reactivity of molecular iodine, the analogy can be extended.

Figure 0121

Reactivity of recurring molecular units.

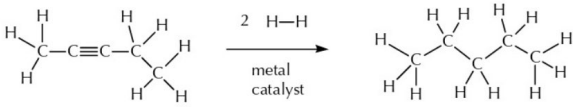


The reactivity of recurring molecular units, such as triple bonds, does not depend on the particular molecule, and analogous reagents, such as molecular bromine and molecular iodine, show comparable results.

Having guidelines are important because they give you permission to extend the scope of the chemical reaction to new molecules. The changes observed for these carbon-carbon triple bonds not only apply to reactions with molecular halogens, as in the previous examples, but also to the reactions between these same triple bonds with molecular hydrogen, when in the presence of an appropriate metal catalyst (Figure 0122).

Figure 0122

Observed reactivity analogies.



Observed reactivity analogies can extend through other parts of the periodic table, as the reaction between molecular hydrogen with triple bonds is comparable to those of molecular halogens.

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B. Atoms, Molecules, and Ions

Understanding chemistry relies on a precise use of symbolism and language, in great part because we are describing the world on a scale that cannot be directly visualized. If you see or hear the word "hydrogen," it could be referring to many different things, and so the context of the word matters—how it is being used, what the surrounding words or other symbols might mean.

"Hydrogen" could be referring to the common hydrogen atom, the element made up of one proton and one electron. The hydrogen nucleus is symbolized by an "H" (meaning "an element with 1 proton"), and if you mean to refer to the hydrogen atom, then you want to include that single valence electron from the unfilled shell along with the letter, namely "H•".

Atomic hydrogen is the most common element in existence and is estimated to make up over 90% of the known atoms in the universe. Elemental atomic hydrogen is actually a collection of atoms that all share the property of having one proton, so even saying "atomic hydrogen" is really not enough to specify just one thing. Atomic hydrogen with one proton, one electron, and no neutrons has an atomic mass of 1, and its name is "protium" (ca. 1930s, meaning "single" or "first"), and it is more accurately symbolized by "1H" to represent its mass. This is the most common form of atomic hydrogen, making up 99.98% of the natural abundance. Almost all of the remaining atomic hydrogen has one proton, one electron, and one neutron, and its atomic mass of 2 gives the name "deuterium" (also from the 1930s, meaning "two" or "second"). Deuterium is symbolized either by "2H" or "D". There are trace amounts of atomic hydrogen with two neutrons in its nucleus, and this is "tritium" (meaning "three" or "third"), and symbolized by "3H" or "T". There are only trace amounts of naturally occurring tritium on earth, and it is also radioactive, and decomposes with a half-life of about 12 years. Collectively, these three are the isotopes of atomic hydrogen ("iso-" meaning "the same" or "equal" as it did in the word isomer, and "-tope" being derived from "topology" meaning "place" or "location"; isotopes, in other words, occupy the same location on the periodic table). In all of these atoms, a single, positively charged proton accompanies a single, negatively charged electron, and so the atom is formally uncharged (charge = 0).

The word "hydrogen" might also refer to molecular hydrogen, H_2, the diatomic molecule that is formed from two hydrogen atoms with a shared (covalent) electron pair, one from each of the hydrogen atoms ("H:H" or "H-H").

Assessing Stability: For the purposes of assessing stability, each atom can claim both of the electrons in a shared pair plus any nonbonding electrons. Thus, both of the hydrogen atoms in molecular hydrogen can claim two valence electrons, which is the closed shell value in the first row of the periodic table (Figure 0123). A first row element having the 2-electron closed shell configuration of helium satisfies the "duet rule."

Figure 0123
Assessing stability.

For assessing stability, the full valence set is included for each atom, so each hydrogen atom can claim a closed shell (helium duet) electron configuration.

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Assigning Formal Charge: For the purposes of assigning formal charge, however, each atom can only claim half of the electrons in a shared pair, plus all of any nonbonding electrons. Each of the hydrogen atoms in molecular hydrogen, then, can only claim one electron for the purpose of assigning a formal charge to the atom. If an atom in a molecule claims the same number of electrons as in its atomic state, where the number of electrons equals the number of protons, then the formal charge is zero (an uncharged atom). If the number of electrons claimed by the atom is greater than that number, then those excess electrons give the atom a formal negative charge. And if the number of electrons claimed by the atom is less than that number, then the positive charge of the nucleus is not being completely matched, and a formal positive charge is assigned. Thus, each of the hydrogen atoms in molecular hydrogen can claim one electron, which matches the normal valence for the uncharged hydrogen atom, and so both of the hydrogen atoms in molecular hydrogen have a formal charge of zero (Figure 0124).

Figure 0124

Assessing formal charge.

For assessing formal charge, nonbonding electrons and only half of the shared electron pairs can be claimed by each atom, so each hydrogen atom can claim one electron, the same as in the atomic state and so uncharged (formal charge = 0).

The word "hydrogen" might also refer to various hydrogen ions. Ions are charged atomic or molecular entities (often called "atomic or molecular species"). As described in the previous paragraph, formal charges on atoms result with the number of electrons claimed by the atom being different from the number associated with its uncharged valence form. A hydrogen atom with two electrons ("H:") can claim both for the purpose of assigning charge, because they are a nonbonded pair. A hydrogen atom claiming two electrons has one more electron (e-) than its normal uncharged valence number (1 electron) and so "H:" carries a negative charge. This atomic species is called the hydride anion (H:-). For the purpose of assessing its stability, it has a closed shell (duet) electron configuration. A hydrogen atom with no electrons has the net +1 charge of the proton (p+). The number of electrons this atom can claim is zero, and that is one electron less than its uncharged state. The hydrogen atom cation is symbolized as "H+" and is quite rightly referred to as "proton" (Figure 0125). Added neutrons (n^0) do not change the chemical identity of an atom, and all atoms with one proton are hydrogen atoms. Hydrogen atoms with one neutron (atomic mass = 2, and so ^2H, deuterium; also "D") and two neutrons (atomic mass = 3, and so ^3H, tritium; also "T") are the other two isotopes of hydrogen ("isotope" meaning the "same place" on the periodic table).

Figure 0125

The hydrogen family.

hydrogen atoms (isotopes)

H• ^1H (protium, H: $1p^+$, $1e^-$, $0n^0$; 99.98% abundance)
^2H (deuterium, D: $1p^+$, $1e^-$, $1n^0$; 0.02% abundance)
^3H (tritium, T: $1p^+$, $1e^-$, $2n^0$; trace, half-life ~ 12 years)

hydrogen molecule

H_2 H:H H-H

hydrogen ions

H^+ ($1p^+$; $0e^-$; open shell, almost never observed unassociated)
$H:^-$ ($1p^+$, $2e^-$; closed shell, available in ionic compounds, e.g., $Na^+ H:^-$)

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C. Words and Other Symbols Are Invented and Adapted to Capture Meaning

The previous section not only illustrates a significant principle in understanding chemistry, but also in understanding almost anything that we try to communicate. This principle is that our symbols rarely have intrinsic meaning, but rather that meaning is something that we assign to symbols. Symbols are placeholders or representations for meaning.

Consider every word in this sentence… in this paragraph… in this chapter. None of them have any intrinsic meaning. If you had never learned that the word "cat" represents a furry feline, you could certainly never learn anything about a cat from the letters c, a, and t. Sometimes symbols carry literal meaning. The crossing of four lines "𝍸" counts off five things. But other symbols representing five things ("5" or "V" or "五") do not carry such useful clues. You might think that "H_2O" tells you a lot about water. And it is true that there is a specific symbolism of chemistry (the ratio of atoms in the molecule) that is contained in that symbol, which is a lot more than you learn from the symbol "water," yet everything else you know about water (liquid at room temperature, boils at 100C, wet, dissolves salts, and so on) cannot be derived from either of these symbols. This meaning is learned and assigned. As is true with language, chemistry is a semiotic system (semiotics: the field of symbols and their meanings).

In describing chemical phenomena, the point has been made already that humans often attempt to communicate something useful when they invent new words. Examples of words that were invented to capture specific chemical meaning are scattered throughout this chapter: halogen (bringer of salt), stoichiometry (counting elements), isotopes (same locations), isomers (same parts), chlorine (green), valence (value), and so on.

In some of the earlier examples of balanced equations for chemical reactions, there were cases where two starting materials combined to give one product, and that one product contained the sum of all the atoms in those two starting materials. Rather logically, these reactions were (and still are) referred to as "addition reactions" (Figure 0126).

Figure 0126
Addition reactions from previous examples.

$$C_3H_4 + 2\,Br_2 \longrightarrow C_3H_4Br_4$$

$$C_5H_{10} + H_2 \xrightarrow[\text{catalyst}]{\text{metal}} C_5H_{12}$$

In Figure 0126, the word "addition" is being used quite descriptively to represent the elements "adding together" in these equations. The supposed intent is to communicate something useful about what happens in these reactions in contrast with others. "Addition" becomes a fundamental classification for organic chemical reactions.

What is unstated in the equations in Figure 0126 is that attempts to combine these products ($C_3H_4Br_2$ and C_5H_{12}) with more bromine and hydrogen, respectively, did not yield any more addition of these elements to the organic molecule. Consequently, these products were referred to as having "saturated" structures, another co-opting of a common word to express the idea that, like a sponge filled with water, the structures could hold no more atoms. If $C_3H_4Br_2$ and C_5H_{12} represent saturated molecular structures, then C_3H_4 and C_5H_{10}, from which they came, were immediately called "unsaturated" structures. Using these terms, a sentence such as this is loaded with chemical meaning: the property of an unsaturated

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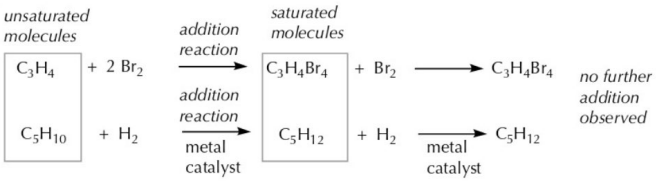
structure is that it can undergo addition reactions until the point at which it is saturated, and addition reactions stop (Figure 0127).

Figure 0127

Structure considered "saturated."



Historically, no further addition meant that the structure was considered "saturated."

A reminder here that there are underlying chemical ideas for all the observations given in this chapter, so far, and it will take some work to develop those ideas. The purpose of this chapter is to illustrate how humans began to define and develop the relationship between organic molecular structure and organic chemical reactions. So many of the ideas, even so far in this first chapter, provide a foundation of useful principles that will recur over and over throughout your study. The most basic principles (counting atoms to balance an equation, keeping track of formal charges, recognizing all the parts of a structure that did not change during a reaction, being able to read the meaning in a word such as "addition reaction" when you see it) will only get more useful as time goes on and more complex ideas are introduced.

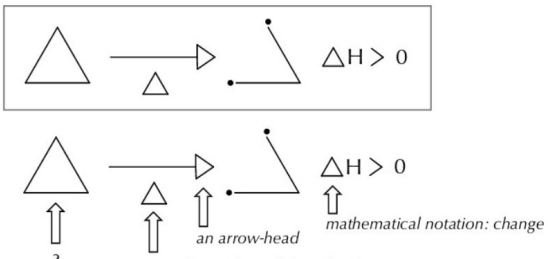
D. Line and Condensed Abbreviation Conventions for Representing Organic Molecular Structure

The interpretation of symbols is also highly dependent on their surroundings (context). Identical symbols can mean different things depending on what surrounds them and how they are being used. In language, homographs are words that are spelled the same way but whose meaning varies according to the pronunciation. A group of laborers might be unionized (union-ized), while a molecule might be in its union-ized (un-ionized) form. And the more you think about the number (num-ber) of atoms or molecules in a mole, the number (numb-er) and number your mind might become. And please: do not desert me in the desert!

In the following statement (Figure 0128), an identical triangular shape is used in four distinctively different ways. Depending on your background, you probably recognize how two or three of these symbols are being used (i.e., what they mean).

Figure 0128

A statement with four triangular shapes



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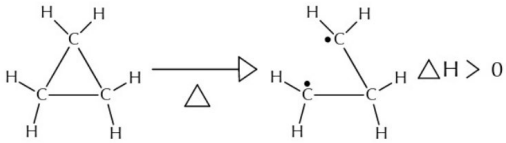
The fourth use of the triangular shape (the large one in the figure) is likely unfamiliar to you, and it is your first truly unique lesson from the field of organic chemistry: the line abbreviation convention for representing organic molecular structure. When a person experienced in this notation looks at that statement, this is what they see in their mind's eye (Figure 0129).

Figure 0129

Explicitly decoding the organic chemistry line abbreviations.



When this C_3H_6 molecule is heated, one of the carbon-carbon bonds breaks to give one electron with each carbon atom. The process is endothermic.

There are only three rules for using this notation system:

(1) the carbon atom symbol can be excluded as long as its position can be inferred from the surrounding bonds, and all other atomic symbols except hydrogen must be shown;

(2) the hydrogen atom symbols on the inferred carbon atoms, and their bonds, can be excluded; but

(3) the hydrogen atom symbols must be included when attached to any atomic symbol that is depicted, including carbon.

For the C_3H_6 molecule in this example, all three of the carbon atoms can be inferred from the intersection of the bonds, and so the symbol for the carbon atoms can be excluded. The hydrogen atoms and their bonds can be excluded. If the carbon atom symbol is shown, however, the hydrogen atoms and their bonds must also be shown. The first three drawings in Figure 0130 are all correct, while the fourth and fifth ones are incorrect representations for this C_3H_6 molecule.

Figure 0130

Correct and incorrect representations for the cyclic C_3H_6 molecule.

The three C_3H_5ClO isomers from Figure 0109, as represented using the line abbreviation notion, are shown in Figure 0131, including their complete abbreviations, some correct partial abbreviations, and some incorrect abbreviations.

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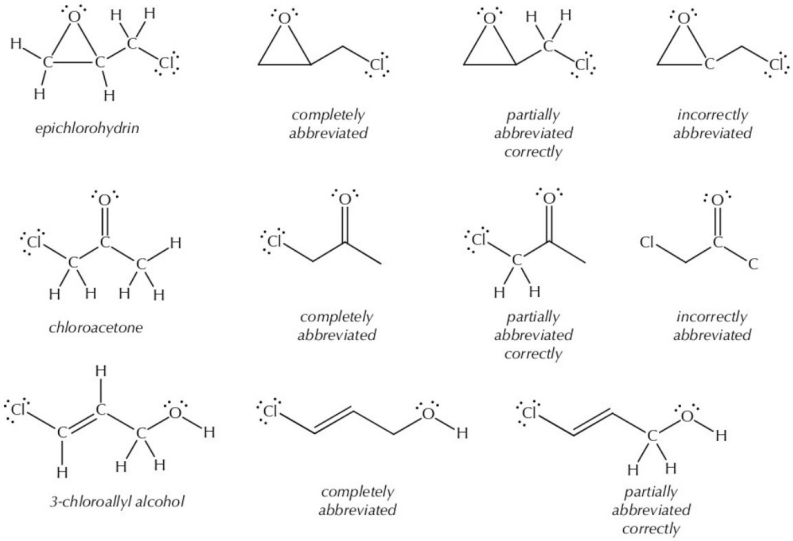
Figure 0131

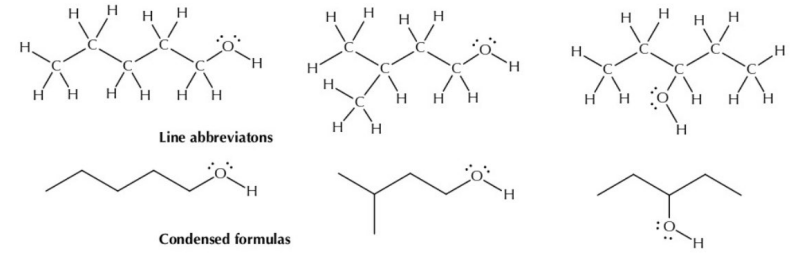
Correct and incorrect representations for three C_3H_5ClO molecules.



A molecular formula such as $C_5H_{12}O$ is highly condensed, but with no specific structural information, it represents a large collection of different structural isomers. Communicating the connectivity for a specific structural isomer can be done with a fully drawn Lewis structure, with a line abbreviation, and also by using a condensed formula abbreviation method (Figure 0132).

Figure 0132

$C_5H_{12}O$ structural isomers.



Three examples of $C_5H_{12}O$ structural isomers shown using: top row—full Lewis structural representations; middle row—line abbreviation representation; bottom row—condensed formula representation.

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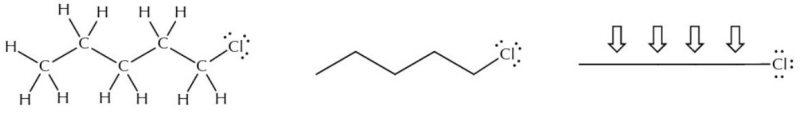
You may have already noticed, and you can see it in Figure 0132, that lines of atoms are commonly represented in a "zig-zag" fashion. This "v-shaped" drawing convention allows the reader to see where the bonds are intersecting in ways that would be impossible if the line of atoms was shown linearly (Figure 0133).

Figure 0133

The "zig-zag" drawing convention.



Lewis Structure correct *line abbreviation correct* *incorrect*

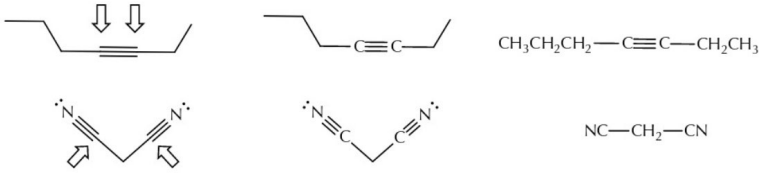
The "zig-zag" drawing convention allows a reader to keep track of the atoms.

There are a few circumstances where, because of geometrical constraints that will be described fully in the next chapter, the string of atoms is drawn linearly because the molecular geometry is known to be linear. Two of these are commonly encountered.

Triple bonds. The two atoms attached to the atoms of a carbon-carbon triple bond exist in a four-atom linear geometry, and the atom attached to the carbon atom of a carbon-nitrogen triple bond creates a three-atom linear geometry. Sometimes the carbon atoms of the triple bond are included explicitly for clarity (Figure 0134).

Figure 0134

Alternatives for representing triple bonds.



full line abbreviation correct *partial line abbreviation correct* *condensed formula correct*

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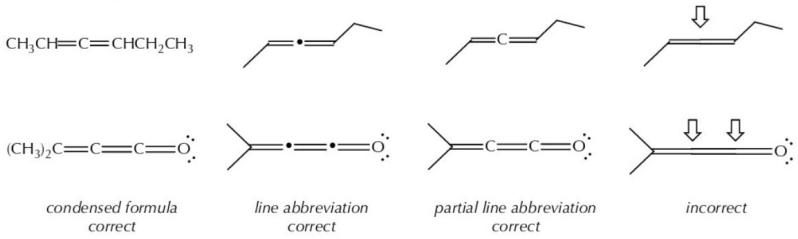
Cumulative double bonds. The atom shared by two directly bonded double bonds has a linear geometry with respect to its two attached atoms. If there are over two double bonds in an uninterrupted strand, then this generalization extends to each pair. Sometimes the carbon atom is included for clarity, sometimes a "•" is used to represent the carbon atom (Figure 0135).

Figure 0135

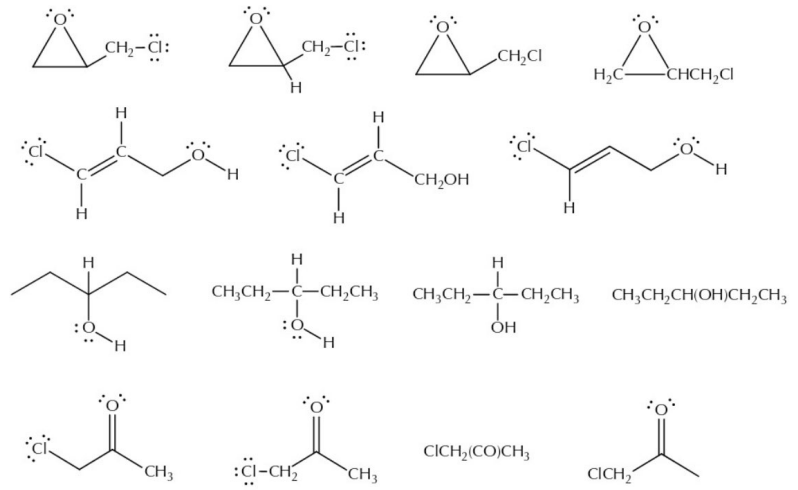
Alternatives for representing cumulative double bonds.



The representational methods described in this section are not only used interchangeably, but they are often combined as a way to emphasize or make explicit some features of a molecule while de-emphasizing others (Figure 0136). The choice is up to the person who is drawing the structure and is based on the story that is being told. The conventions for when to use which type of drawing are not rule driven (as long as the part of the structure you are drawing is drawn correctly), but rather a matter of aesthetic convention that you will start to adopt, over time, with practice.

Figure 0136

Examples of molecules with mixed representations (all shown correctly).



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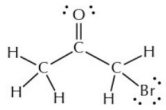
PRACTICE QUESTIONS

1.18 Bromoacetone is the name of a compound with a unique connectivity (shown below; there are no other structural isomers). Tribromoacetone, on the other hand, is the name of a compound with two structural isomers. Draw the Lewis structures for the two different tribromoacetone isomers (compounds 1.18A and 1.18B).

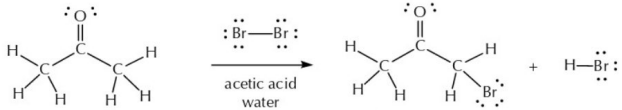


bromoacetone

1.18A	1.18B

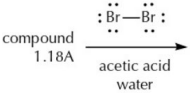
tribromoacetone isomers

1.19 Bromoacetone can be prepared by treating acetone with 1 equivalent of molecular bromine (Br_2) in a solution of acetic acid in water (see below). When the tribromoacetone molecules you drew in question 1.18 (compounds 1.18A and 1.18B) are treated with 1 equivalent of molecular bromine (Br_2) in a solution of acetic acid in water, an analogous reaction takes place, forming tetrabromoacetone.
(a) Draw all of the tetrabromoacetone products that can be formed starting from 1.18A.
(b) Draw all of the tetrabromoacetone products that can be formed starting from 1.18B.
(c) Do these two reactions give the same or different set of possible products? Explain.

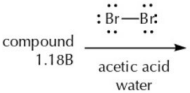


acetone *bromoacetone*

(a)



(b)



(c)

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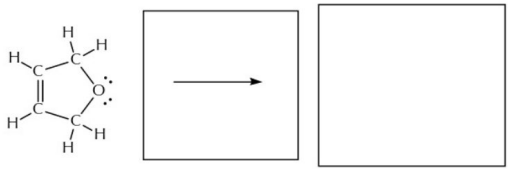
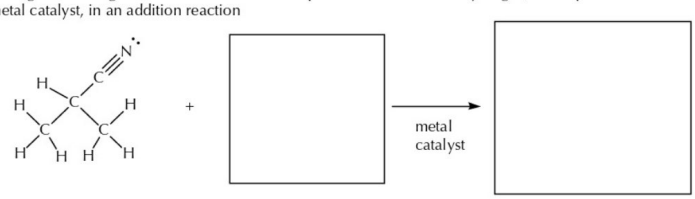
1.20 Examples of addition reactions are provided for reference in various parts of the previous section. Provide the structures for the missing components of the following addition reactions. Use unabbreviated structures and include nonbonding electron pairs. All of the atoms are uncharged and have closed shell configurations.

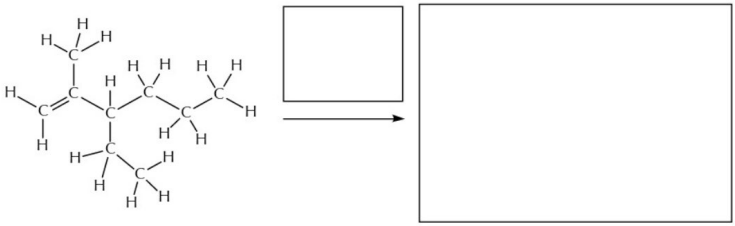
(a) the organic starting material combines with 1 equivalent of hydrobromic acid in an addition reaction



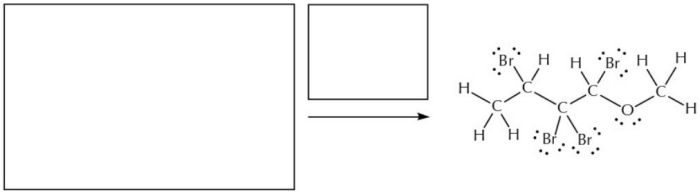
(b) the organic starting material combines with 2 equivalents of molecular hydrogen, in the presence of a metal catalyst, in an addition reaction



(c) the organic starting material combines with 1 equivalent of molecular iodine in an addition reaction



(d) the organic starting material combines with 2 equivalents of molecular bromine in an addition reaction



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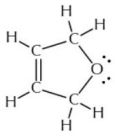
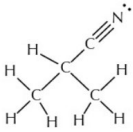
1.21 Draw the four structures that were shown in question 1.20 using the line abbreviation method (include nbe).

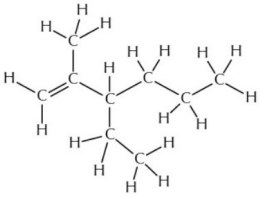
(a)



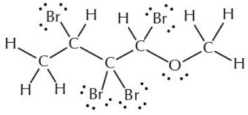
(b)



(c)

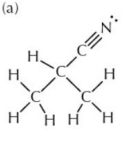


(d)

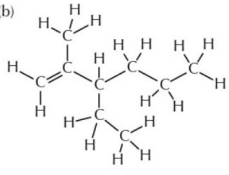


1.22 Using the condensed formula method, in which all of the atoms are shown, provide structures that represent these two molecules. There are many correct options, so this is a good problem to share and compare your answers with other students.

(a)



(b)



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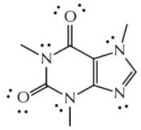
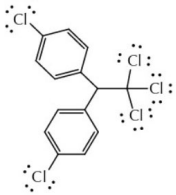
1.23 What are the molecular formulas for these molecules?

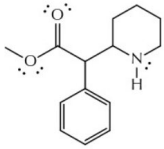
(a) caffeine



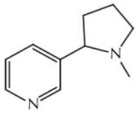
(b) DDT



(c) methylphenidate (Ritalin)

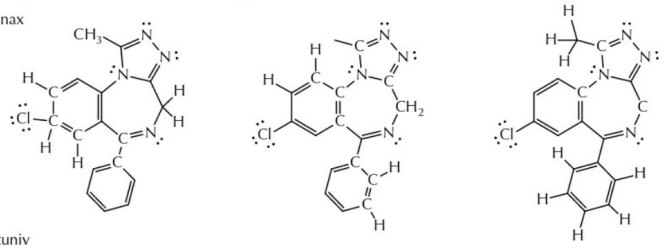


(d) nicotine

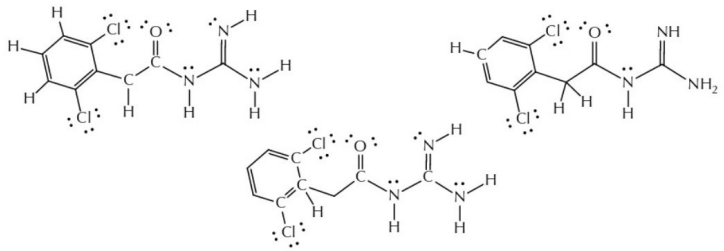


1.24 There are three representations shown for both of the following molecules (Xanax, a common sedative, and Intuniv, used to treat ADHD). All of the drawings are shown using a combination of the representational systems. Some of the drawings are completely correct (although they may look a little strange, as long as the conventions are being followed correctly, then these are not errors), and some of them have one or more errors. All atoms are uncharged, closed shell, and should display their nonbonding electrons. Find the actual errors in these drawings and correct them (there may be more than one correct strategy to correct these errors).

(a) Xanax



(b) Intuniv



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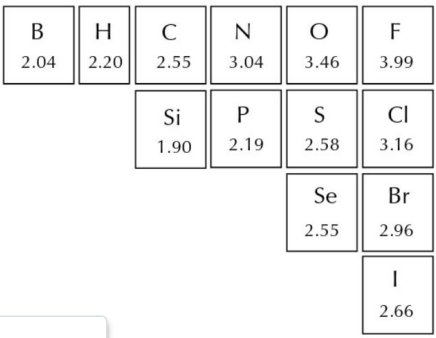
1.4 The General Chemistry of the Organic Main Group Elements

A. Closed Shell Valence Bond Molecular Structure and Properties

Closed Shell Electron Configuration. Much of the behavior of atoms, both in bonding and in reactivity, and particularly for the organic main group elements, is dictated by the attainment of closed shell electron configurations. In the first row (H, He) this means having 2 valence shell electrons (the duet rule). In the second row, for the s-block (Na, Be), this means losing electrons to get the helium configuration, and for the p-block (B, C, N, O, F, Ne), this means having 8 valence shell electrons (the octet rule). Elements in the third row mimic the properties of those in the second row, but the octet of electrons can be exceeded in hypervalent bonding, where participation with the d-level can begin to take place. In later studies of chemistry, you may encounter the 18-electron rule that governs basic bonding properties in the fourth, fifth, and sixth rows.

Electronegativity. Negatively charged electrons are attracted to the positively charged nucleus by an electrostatic force. An electron will be attracted to a more positive charge over a less positive charge, and it will be more attracted when it is closer to the positive charge than farther away from it. The electronegativity of an element is a measure of how relatively attracted a given electron is to its nucleus. In a row of the periodic table, the relative placement of electrons is about the same distance from the nucleus, so as you move from left to right, and the positive charge in the nucleus is increasing by +1 with each element, the attraction for the electron goes up and (a) the electronegativity of atoms therefore increases as you move from left to right in a row, and (b) the size of atoms decreases slightly as you move from left to right because the electrons are held a little more tightly. As you move down a column on the periodic table, there is a conflict in criteria. The nucleus is significantly more positive, but (a) some of the positive charge is diminished by the intervening electrons, and (b) the lower you move in a column, the significantly farther away from the nucleus the electrons are sitting. As a result, the interaction between the electrons and the nuclei of larger atoms is poorer than for the smaller ones above it on the periodic table, and so the electronegativity decreases as you move down a column. Fluorine, then, has the highest electronegativity because it has the greatest positive charge that a new electron can feel (Figure 0137).

Figure 0137
Electronegativity values (Pauling scale).



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1.4 The General Chemistry of t...
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Formal Charge. As described in Section 1.3, atoms in molecules are uncharged when the number of electrons that can be claimed by that atom (all nonbond electrons plus half of any shared pairs) is equal to the number of protons that the atom possesses. A convenient corollary to this uncharged, closed shell generalization for the organic main group elements (carbon atoms with 4 bonds, nitrogen atoms with 3 bonds and 1 nbe pair, etc.) is that atoms with other than these descriptions must be charged, open shell, or both.

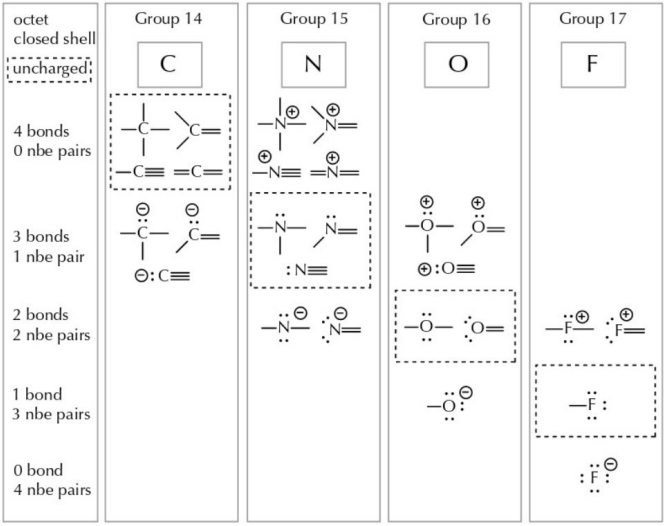
Starting with the second row atoms that maintain their closed shell configurations (Figure 0138), you can see the distinctive bonding patterns and how that relates to different elements and their formal charges. The open lines on the atoms in this table are called "incipient bonds," that is, an indication of the number and kind of shared electron bonds that each atom could form.

Examine, for instance, the second row ("3 bonds, one nbe pair"). Carbon atoms have 4 valence electrons, and a carbon atom with 3 bonds and one nbe pair claims five electrons [2 (1 nbe pair) plus 3 (half of the 6 electrons in the 3 bonds)]. Those 5 claimed electrons are one above the valence (uncharged atom value) of 4, so the carbon has a "-1" charge. Nitrogen atoms and oxygen atoms with 3 bonds and 1 nbe pair also claim 5 electrons, but the nitrogen valence is 5 and the oxygen valence is 6, and so the nitrogen atom is uncharged and oxygen atom is positively charged.

Although not strictly impossible, formal charges on these elements, outside of the [-1, 0, +1] range, are rare and generally either unstable or highly reactive (Na_2O exists, for instance). Unless there is experimental evidence to support the idea, organic main group atoms with charges outside of this [-1, 0, +1] range are presumed not to exist or be of significant importance.

Figure 0138

Charged and uncharged atoms with closed shell octets.



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Bonding. The simplest guideline for understanding chemical affinity (the reason why atoms form molecules) is for the atoms to attain closed shell electron configurations.

Ionic Compounds. The chemistry of the s-block elements, in particular, is driven by transferring their valence electrons to other elements and achieving closed shell electron configurations. When elemental sodium releases its single valence electron it becomes the sodium cation and possesses the same electron configuration as neon. Ionic compounds are made up of a balance of positive and negatively charged ions. The ions in ionic compounds do not need to be derived purely from single atoms (sodium ions, calcium ions, or bromide ions) but can also be multiatomic with one of more atoms bearing a formal charge (such as ammonium ions, hydroxide ions, or carbonate ions). Ionic compounds should generally be drawn as the two (or more) ions, either in a condensed molecular formula, or as discrete ions, and not as atoms having a fixed pair of shared electrons, which they do not. Even the term "ionic bond" is deceptive because ionic compounds, in their solid state, exist in extensive crystal lattices, not as simple binary compounds (see Figure 0139 for examples of ionic compounds and their depictions).

Nonpolar Covalent Compounds. For hydrogen and the other organic main group elements, shared electron pair "covalent" bonds are overwhelmingly the most common observation. If the two atoms are identical, the two nuclei attract the shared electrons equally; the bond is called nonpolar covalent (Figure 0139).

Polar Covalent Compounds. If the two atoms are not identical, the two nuclei attract the shared electrons unequally, where we imagine the electrons being held closer to the more positive (more electronegative) nucleus; the bond is called polar covalent. In the HF bond, for example, we imagine that the shared electron pair is distributed unequally between the two atoms because the nucleus of the fluorine atom (nuclear charge = +9) is better at attracting electrons compared with the nucleus of the hydrogen atom (nuclear charge = +1). This unequal sharing of the electrons can be symbolized by showing a "partial negative charge" (δ-) on the fluorine atom, and a "partial positive charge" (δ+) on the hydrogen atom (Figure 0139). Depending on the pair of atoms and the difference in their electronegativity, there is a range of polarities for these bonds, and this difference can influence how the bond behaves and/or how the molecule reacts. Many polar covalent bonds with only small differences in electronegativity (less than about 0.5) behave more or less like nonpolar bonds. In organic chemistry, CH bonds are typically treated as being nonpolar unless there is some experimental reason to treat them as polar.

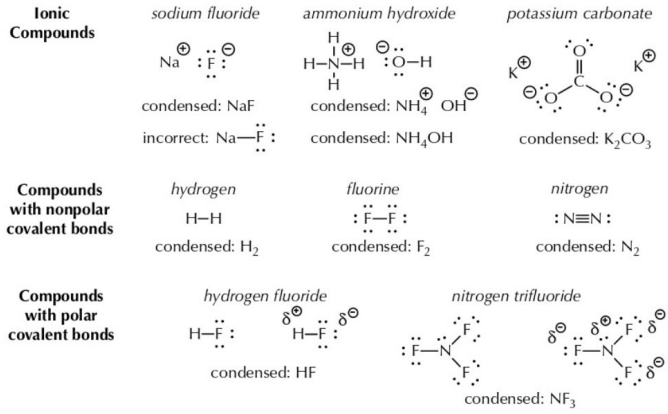

Figure 0139
Representative ionic, nonpolar covalent and polar covalent compounds, along with condensed formulas and indications of full and partial charges.

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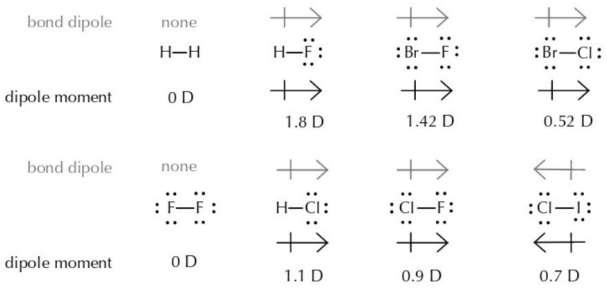
Bond Dipoles and Molecular Dipole Moments. As scientists were debating about the nature of the chemical bond in the early 20th century, Peter Debye, in 1912, developed the idea that bonds in unsymmetrical molecules would have unequal charge distributions, and that the strength of this electric field could be measured. For simple, diatomic molecules, the electrical dipole formed by the two atoms in the bond (the bond dipole) would also be the same as a measurable molecular property, the molecular dipole moment. In experiments, these predictions were borne out. Molecules such as molecular chlorine or molecular hydrogen have completely symmetrical, nonpolar covalent bonds, and molecular dipole moments equal to zero (the unit for dipole moment is the Debye, so "0 D"). HF has a molecular dipole moment of 1.8 D, while the value for HCl is 1.1 D. The molecular dipole moment of the ionic compound KBr has been measured as 10.4 (it exists as a diatomic molecule in the gas phase). The typical symbolism for a molecular dipole moment is an arrow that points to the negative pole of the molecule with a crossed line at the positive pole (Figure 0140).

Figure 0140

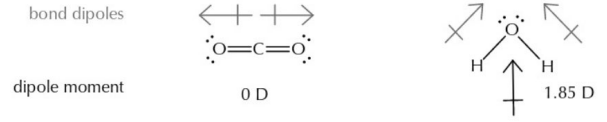
Diatomic molecule, their bond dipoles and their dipole moments.



The dipole moments for molecules with more than two atoms can also be measured, and these are considered to be the mathematical and geometrical sum of the contributions from the individual bond dipoles, which cannot be measured. Overall molecular geometry matters, and for simple triatomic molecules, useful experimental information about the molecular geometry can be inferred from the measured dipole moments. For example, the molecular dipole moment for carbon dioxide (CO_2, connectivity OCO), is 0 D, while that for water (H_2O, connectivity HOH) is 1.85 D. The sensible inferences from these data are that the three atoms of carbon dioxide are arranged linearly, and the two CO bond dipoles cancel, while the three atoms of water are bent (Figure 0141).

Figure 0141

Triatomic molecules, their bond dipoles and their dipole moments.



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B. Open Shell Atoms and Their Reactivity

Achieving a closed shell electron configuration is the most significant factor in the bonding of atoms within the organic main group elements, and many others. Although the duet and octet electron configurations of first and second row elements cannot be exceeded, there are examples where molecules containing an atom with an open shell, sextet configuration are known to exist. Perhaps unsurprisingly, the reactivity of these atoms is defined by achieving a closed shell configuration.

Among the organic main group elements, boron, carbon, and nitrogen are most often seen with open shell, octet forms. To be clear, these forms are usually highly reactive and can have extremely short lifetimes, yet they are often proposed to exist to help explain how some observed reactions take place. A summary of the most commonly observed sextets for these three atoms is given in Figure 0142, which also includes a set of analogous octet forms for comparison.

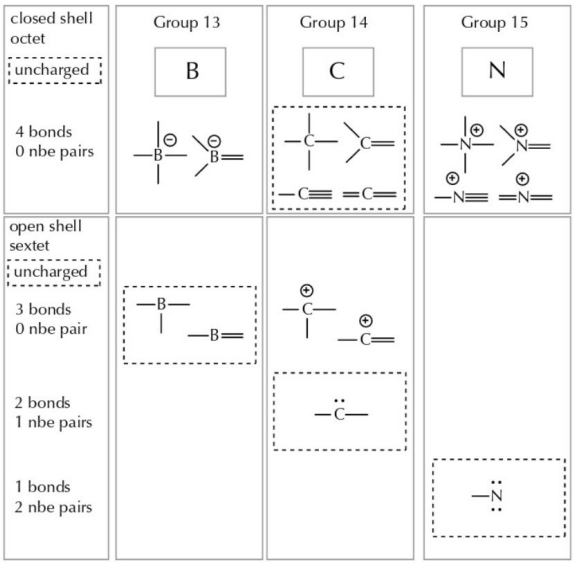

Figure 0142
Common open shell sextet forms.

Common open shell sextet forms observed for boron, carbon, and nitrogen, along with a set of comparable octet forms.

Boron. Boron is the lightest Group 13 element and has 3 valence electrons. Boron can form 3 covalent bonds and so, in its uncharged state, has an open shell sextet. The simplest molecule that meets these conditions is BH_3, named borane. Covalent bonds between boron and all of the other organic main group elements also exist [e.g., $(CH_3)_3B$, $(CH_3O)_3B$, BF_3]. Among these three columns, the boron-based compounds are by far the most common.

Carbon and Nitrogen. Carbon and nitrogen atoms with open shell sextets typically have extremely short lifetimes and are highly reactive. In the second column of Figure 0142, there are two examples involving carbon atoms: the positively charged version called "carbocations" and the uncharged version called "carbenes." By analogy, the uncharged nitrogen atom version is called a "nitrene."

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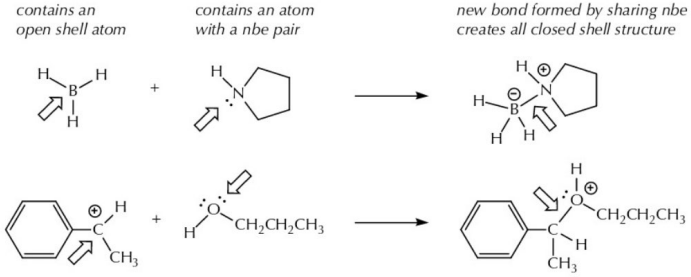
Open shell boron atom and carbocations both have three bonds and no electron pair, and they share a common reactivity. The open shell atom forms a new 2-electron covalent bond with an atom carrying an available nonbonding electron pair, thereby achieving a closed shell electron configuration. The examples in Figure 0143 illustrate this principle.

Figure 0143
Examples of open shell atom reactivity.

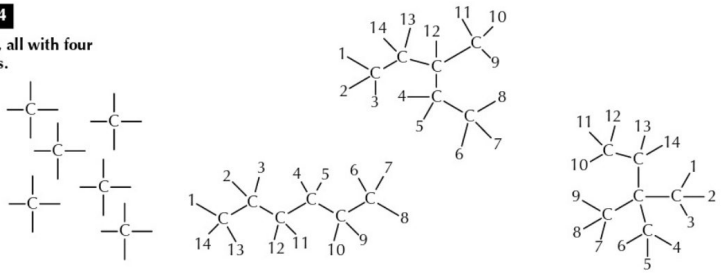

contains an open shell atom
contains an atom with a nbe pair
new bond formed by sharing nbe creates all closed shell structure
CH2CH2CH3
CH3

C. Structural Information Derived from Molecular Formulas: Units of Unsaturation

Hydrocarbons. The reliably predictable bonding patterns of the organic main group elements enables you to start with a molecular formula, such as C_6H_{14}, and then confidently create an array of molecules whose atoms are all uncharged and have a closed shell electron configuration.

Because of the predictable bonding, there are also a maximum number of hydrogen atoms that can be associated with any given number of carbon atoms. This maximum number occurs when there are only single bonds between the carbon atoms and no rings of atoms in the structure. This can be convincingly illustrated with a few examples. In Figure 0144, a set of six carbon atoms is shown, with each of them ready to form four single bonds. These six carbons might be combined in numerous ways, but as long as there are no multiple bonds (double, triple) and as long as there are no carbon rings, the number of open bonding sites is always 14.

Figure 0144
Six carbons, all with four single bonds.



Six carbons, all with four single bonds, when connected together without forming a ring, always leave 14 available bonding sites.

The pattern is most clear when the carbon atoms are linked together in a linear chain. Each carbon atom has two available bonding sites, and the ones at each end have three sites, just as is seen in the condensed molecular structure: $CH_3CH_2CH_2CH_2CH_2CH_3$. This relationship (2H per C, plus 2) is a fixed ratio as long as (a) the carbon atoms are all closed shell and uncharged, (b) the resulting structure has no multiple

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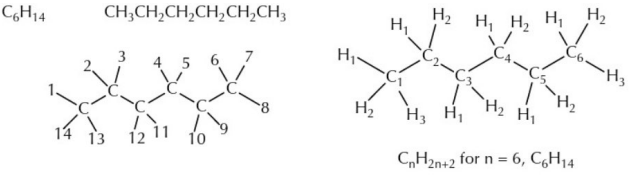
bonds or rings. This ratio can be expressed mathematically: for every "n" carbons (n = an integer), there are "2n+2" bonding sites. In the example in Figure 0145, hydrogen atoms occupy all of the bonding sites. The molecular formula that began this discussion, C_6H_{14}, is consistent with this generalization about the carbon-to-hydrogen ratio C_nH_{2n+2} (n = 6, and 2n+2 = 14). Molecules with the C_nH_{2n+2} molecular formula are called saturated hydrocarbons. "Hydrocarbon" refers to a molecule with only carbon and hydrogen atoms in it, while "saturated" (Section 1.3C) historically referred to a molecule that could not undergo addition reactions after having undergone that reaction already. The term saturated has been redefined to mean an organic structure made up of only single bonds and no rings.

Figure 0145
Carbons with four single bonds.

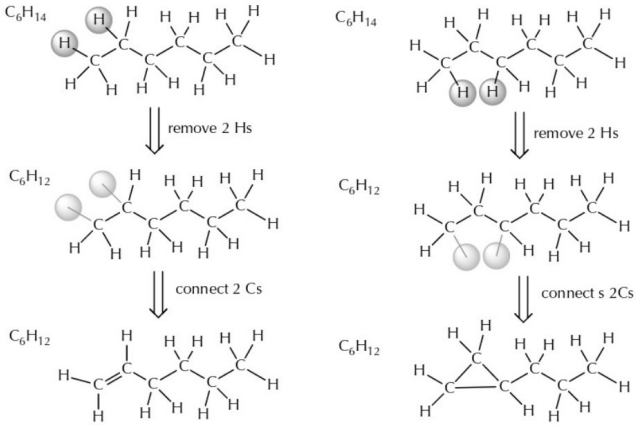


Each of the six carbons, all with four single bonds, when connected together without forming a ring, possess two bonding sites, and two of them possess three.

The consequence of this predictable C-to-H ratio is that it is possible to deduce structural information from a molecular formula. All C_nH_{2n+2} molecules, for instance, represent saturated hydrocarbons.

Starting from a saturated hydrocarbon structure, it takes the removal of two hydrogen atoms to either create a double bond or a ring. Every loss of two hydrogen atoms, starting from a saturated hydrocarbon formula, represents the formation of either a multiple bond or a ring. Each two-hydrogen atom loss, with reference to the number of hydrogen atoms in the saturated hydrocarbon, is called a unit of unsaturation. The imaginary process of losing a pair of hydrogen atoms to form a double bond or a ring is shown in Figure 0146.

Figure 0146
Reducing C_6H_{14} by two hydrogen atoms creates a single unit of unsaturation (a double bond or a ring.)



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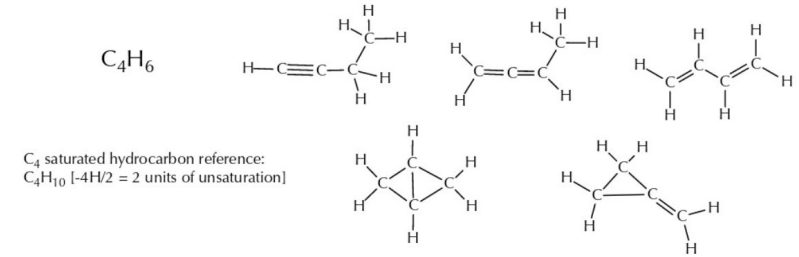
If what you know, experimentally, is the molecular formula of a hydrocarbon (e.g., C_4H_6), you can assess how many hydrogen atoms it is away from the fully saturated number. For 4 carbons (n = 4), there would be 10 hydrogen atoms (2n+2, or 2x4+2) in the saturated hydrocarbon. Instead of 10 hydrogen atoms, there are 6 in C_4H_6, which is a difference of 4 hydrogen atoms from the hypothetical "C_4H_{10}" saturated hydrocarbon reference. Because each unit of unsaturation (a multiple bond or a ring) requires the loss of 2 hydrogen atoms, C_4H_6 (compared with C_4H_{10}) represents 2 units of unsaturation.

The conclusion that C_4H_6 has 2 units of unsaturation means that you can make some basic predictions about the structure from its molecular formula. A C_4H_6 molecule will have some combination of 2 units of unsaturation: (a) two double bonds, (b) two rings, (c) a double bond and a ring, or (d) a triple bond (Figure 0147).

Figure 0147

Examples of some C_4H_6 molecular structures with 2 units of unsaturation.



Expressed as an easily remembered formula, the number of units of unsaturation (#u.u.) in a hydrocarbon whose molecular formula C_NH_Y will be equal to the number of hydrogen atoms in the hypothetical saturated formula (2N+ 2 in C_NH_{2N+2}) minus the number of hydrogen atoms in the actual formula (Y in C_NH_Y), divided by 2 (Figure 0148).

Figure 0148

A mathematical expression for the number of units of unsaturation in hydrocarbon C_NH_Y.

For a hydrocarbon C_NH_Y # u.u. = ("2N+2" - "Y")/2 or $(H_{sat} - Y)/_2$

Organic molecules containing monovalent, divalent, and trivalent heteroatoms. The term "heteroatom" refers to any atom other than carbon or hydrogen in an organic molecule. Among the organic main group elements, there are trivalent heteroatoms (B, N, P), divalent heteroatoms (O, S, Se), and monovalent heteroatoms (F, Cl, Br, I). Thanks to the regular bonding patterns of these atoms, the effect of including heteroatoms on the hydrogen atom count of a hydrocarbon is predictable. In Figure 0149, starting with C_4H_{10}, the effect of including heteroatoms is illustrated.

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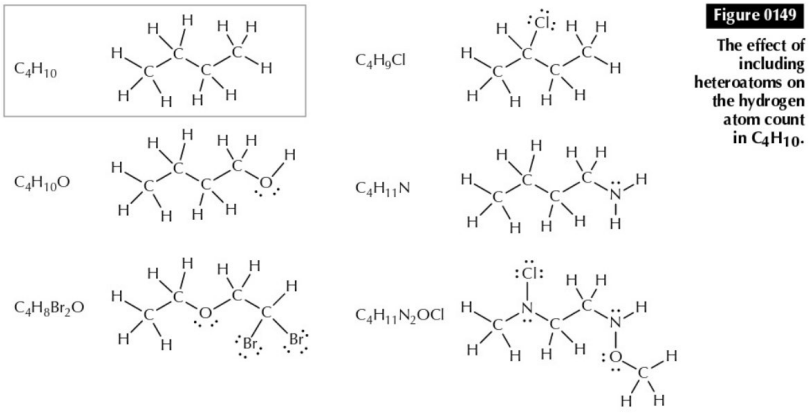

Figure 0149
The effect of including heteroatoms on the hydrogen atom count in C_4H_{10}.

The conclusion, with respect to the corresponding hydrocarbon:

(1) each monovalent heteroatom simply occupies the space of a monovalent hydrogen atom
(2) each divalent heteroatom does not change the hydrogen atom count
(3) each trivalent atom adds an additional hydrogen atom to the structure

The mathematical expression for counting the units of unsaturation only needs to be modified slightly: all monovalent atoms are treated the way hydrogen atoms are, and the total number of hydrogen atoms plus monovalent heteroatoms is subtracted from the "2N+2" value; all divalent heteroatoms can be ignored; and the number of trivalent atoms is added to the "2N+2" number to accommodate the additional bonding site they bring (Figure 0150).

Figure 0150
A mathematical expression for the number of units of unsaturation when heteroatoms are included in a formula.

For an organic molecule $C_NM_mD_dT_t$ with m monovalent atoms M (H and monovalent hetereoatoms), d divalent hetereoatoms D, and t trivalent heteroatoms T, the number of units of unsaturation is given by the following:

u.u. = ("2N+2" - "m" + "t")/2 or # u.u. = $(H_{sat}$ - m + t)/2

$C_6H_4N_2$ #u.u. = [(14 - 4 + 2)/2)] = 6

$C_{15}H_{27}Br_6N$ #u.u. = [(32 - 33 + 1)/2)] = 0

$BNCl_4$ #u.u. = [(2 - 4 + 2)/2)] = 0

CNH #u.u. = [(4 - 1 + 1)/2)] = 2

Units of unsaturation can be used to help you count the hydrogen atoms in a complex organic molecule, when you can easily count the carbon atoms, hetereoatoms, and simply see the units of unsaturation by visual inspection of the structural drawing.

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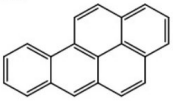
Benzo[a]pyrene is a hydrocarbon and a cancer-suspect agent found in tobacco smoke. By visual inspection, the structure has 5 rings and 10 double bonds, so 15 units of unsaturation. There are 20 carbons, and a saturated C_{20} (N=20) hydrocarbon would have (2N+2) 42 hydrogen atoms. But, this C_{20} hydrocarbon has 15 units of unsaturation, which means 30 (2 x 15) hydrogen atoms fewer than the saturated number. Before actually counting them on the structural drawing, then, benzo[a]pyrene is anticipated to have 12 hydrogen atoms (42–30), which it does (Figure 1051).

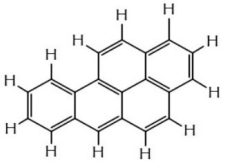
Figure 0151

Units of unsaturation in benzo[a]pyrene.



benzo[a]pyrene

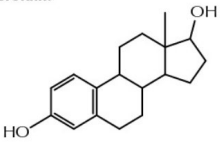
u.u. = 15
C = 20
saturated reference: $C_{20}H_{42}$
- 30 H to account for u.u.
benzo[a]pyrene : $C_{20}H_{12}$



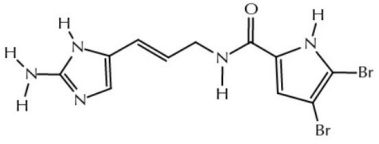
As in the mathematical formula, monovalent heteroatoms reduce the hydrogen count, divalent heteroatoms have no effect, and trivalent atoms add to the hydrogen count (Figure 0152).

Figure 0152

Units of unsaturation in estrogen and oroidin.



u.u. = 7
C = 18
saturated reference: $C_{18}H_{38}$
- 14 H to account for u.u.
[38-14] = 24
estrogen: $C_{18}H_{24}$



u.u. = 8
C = 11
saturated reference: $C_{11}H_{24}$
- 16 H to account for u.u.
- 2 H for 2 Br
+ 5 H for 5 N
[24-16-2+5] = 11
oroidin: $C_{11}H_{11}Br_2N_5O$

D. Using the Curved Arrow Notation to Represent Bonding Changes

Reaction Mechanisms. Organic chemical reactions involve a change in the connectivity of atoms. Bonds are broken; new bonds are formed. Chemists are interested not only in the reactants and the products of a reaction but also in the details, especially the timing, of the bond-breaking and bond-forming processes.

So far, you have seen examples of reactions described by their starting and ending points, but nothing about the details of what happens in between (Figure 0153). These details, called the mechanism of a reaction, are the sequence of bonding changes that would make up the imagined movie about how a set of starting materials is transformed into the observed products.

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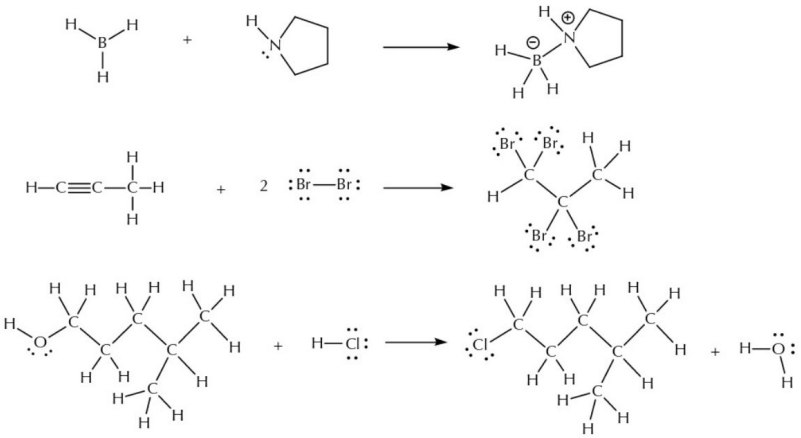
Figure 0153

Three previous reactions illustrated with no detail of the mechanism (stepwise process) for the observed bonding changes.



The first example in Figure 0153 is by far the simplest one. Comparing the two structures of the reactants with the structure of the product, you might describe the change as "the nonbonding electron pair of nitrogen atoms on the left has been used to create a new nitrogen-boron covalent bond on the right." This idea is reasonable, as described in the earlier section on open shell atom reactivity, because the open shell (sextet) boron atom on the left has become a closed shell (octet) atom on the right.

Note the significance of needing to compare the starting and ending points in this reaction to be able to tell the story (mechanism) of what has happened. Looking at only the starting materials, or at only the product, you cannot justify the proposition that it was the BN bond that formed as well as how it formed. As a general principle, we will always provide the full observation when asking you to propose an organic reaction mechanism because this more nearly represents the way that chemists think about the topic of mechanisms.

A reaction mechanism can be studied by making experimental measurements, such as how changing the reaction conditions (concentration, solvent, temperature), or how changing the structures, influences the rate of the reaction or the reaction outcome. This area of organic chemistry is called physical organic chemistry. Sophisticated computational models for atoms and molecules can also be used to explain and/or predict possible outcomes, which is a part of what is called theoretical or computational chemistry. Although direct visualization of molecules, in any traditional sense, is not possible, scientists use this experimental and theoretical information to make inferences and formulate hypotheses about reaction mechanisms … about the timing of the bond change events and why they happen.

Starting in the 1930s, as chemists began to speculate about the mechanisms for organic chemical reactions, they developed a powerfully useful notational system to represent the bonding changes taking place during a proposed reaction mechanism. This drawing system is called the curved arrow notation.

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Curved Arrow Notation. In the reaction between the open shell boron atom and the nonbonding electron pair on the nitrogen atom in Figure 0153, the idea that links the left- and right-hand side of the equation has been stated:

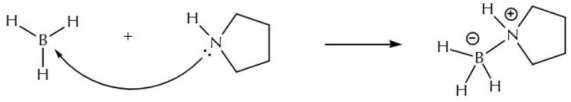
> "the nonbonding electron pair of nitrogen atoms on the left has been used to create a new nitrogen-boron covalent bond on the right"

This description is the proposed mechanism of the reaction. The curved arrow notation is a convenient and graphic restatement of the mechanism that matches this description exactly; no more, no less. A bond forms or breaks by redistributing the involved electrons, and a curved arrow accounts for this change in electron distribution (Figure 0154). Whether a bond is forming or breaking, the curved arrow begins at the electron source and points to its destination. In this case, only a single arrow is needed to account for the formation of the new nitrogen-boron bond using that one nonbonding electron pair.

The curved arrow does not refer to the transfer or relocation of an atom ("this atom now goes here") nor does the curved arrow refer to the transfer or relocation of electrons from being wholly on one atom to being wholly on another (which would be oxidation/reduction reactions, such as Mg metal becoming Mg^{+2} by the complete loss of its valence electrons). Instead, the curved arrow notation is used to represent changes in the state of bonding for atoms. Again, the single arrow in Figure 0154 means one thing: "the nonbonding electron pair of nitrogen atoms on the left has been used to create a new nitrogen-boron covalent bond on the right."

Figure 0154

Curved arrow notation used to describe the mechanism for forming a new nitrogen-boron bond.



"a new covalent bond is formed between the nitrogen atom and the boron atom using the nonbonding electron pair from the nitrogen atom"

Breaking bonds and forming bonds are complementary aspects of the bonding process, and the curved arrow notation can be used equally well for both. Using the 2-electron bond model (which we do!), there are only three ways that a bond can break, in terms of how the 2 electrons are distributed: (1) one of the two atoms could end up with both electrons, and the other atom with none; (2) the other atom could end up with both of the electrons; or (3) each of the atoms could end up with one electron. When a bond breaks so that both electrons end up with one atom, and the other gets none, the process is called a heterolytic bond cleavage. "Hetero-" means "different," and "-lytic" is a common suffix derived from "lyse," which means "to break;" you are likely familiar with the words "hydrolysis," which means "to break apart with water" and "electrolysis," which means "to break apart with electricity." When a bond breaks so that each atom ends up with one electron, the process is called a homolytic bond cleavage.

Hypothetically, one of the CH bonds in methane (CH_4) could be broken in one of three different ways, one of them homolytically and the other two heterolytically. The curved arrow notation can be used to illustrate these processes (Figure 0155). Note that the homolytic redistribution of the electron pair uses a

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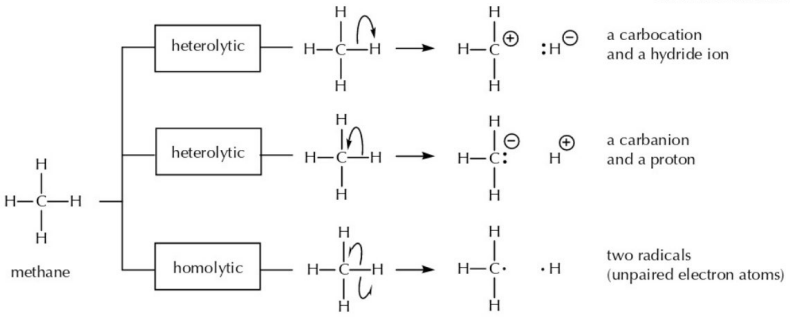
clever version of the curved arrow notation where a single-headed ("fish hook") arrow represents a single electron, as opposed to the full arrowhead that represents an electron pair.

Figure 0155

Curved arrow notation used to describe the three possible mechanisms for breaking the CH bond of methane.

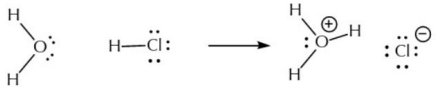


Nearly all of the reactions that you will learn will involve paired electrons (called "polar reactions") as opposed to unpaired electrons (called "radical reactions"). There is a section in Chapter 20 that introduces some of the fundamental ideas about radical reactions.

A one-bond change, with only one needed curved arrow, does not have any timing issues to consider. The bond is either forming or breaking. Most reactions involve more than one change. The familiar chemical reaction between water and hydrochloric acid to give hydronium chloride is shown in Figure 0156. There are two bonding changes in this reaction: the HCl bond breaks and a new OH bond forms. There is also an explicit indication of how the electrons have to be reorganized, because the chlorine atom in HCl becomes a chloride ion, and the oxygen atom ends up positively charged, with three bonds and only one of its nonbonding electron pairs remaining.

Figure 0156

Reaction between water and hydrochloric acid.



Reading this equation from left to right:

The oxygen atom on water uses one of its nonbonding electron pairs to form a third bond with the hydrogen atom of HCl, resulting in the formal positive charge of the hydronium ion; the HCl bond breaks, and the electron pair ends up residing on the chlorine atom as a new nonbonding electron pair, resulting in the formal negative charge of the chloride ion.

Two curved arrows are needed (one to form the new OH bond, one to break the HCl bond). The inventory of bonding changes is only part of the mechanism; the timing of the changes is also a part of the story. With two bonding change events, there are three options for the timing.

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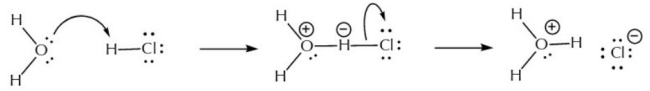
Option 1. The OH bond forms before the HCl bond breaks.
Option 2. The HCl bond breaks before the OH bond forms.
Option 3. The HCl bond breaks as the OH bond is forming.

The way these three options are represented, using the curved arrow notion in combination with drawings, are shown in Figure 0157.

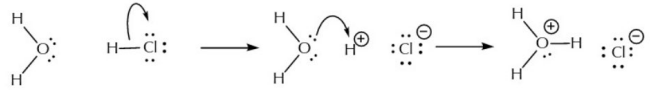
Figure 0157

Three mechanistic options for the reaction between water and hydrochloric acid.

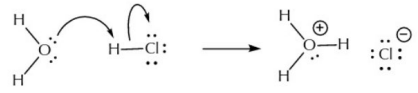
Option 1. The OH bond forms before the HCl bond breaks.



Option 2. The HCl bond breaks before the OH bond forms.



Option 3. The HCl bond breaks as the OH bond is forming.



All three options provide a link between the starting materials and products, but all three options tell a significantly different story about how the bonding changes take place.

The only way to truly select among mechanistic options is with experimental information. And even then, experimental information can never prove a mechanistic option; it can only disprove or rule out an option. Because detailed experimental information is not known for every individual reaction you might need to explain, reasoning by analogy and using sensible general principles are commonly used to propose what a mechanism might be.

Even in the absence of experimental information, option 1 can be rejected summarily. If the OH bond forms first, before the HCl bond breaks, then an anionic hydrogen atom with four electrons is being proposed. Here is a case of using a sensible chemical principle: that anionic hydrogen atom has electrons that exceed the 2-electron limit (duet rule) for closed shell atoms in the first row of the periodic table. This option is simply a bad proposal according to a basic chemical principle that you never see violated.

Choosing between options 2 and 3 is harder to do because there are no closed shell atom violations. In option 2, however, the open shell atom $H^{\cdot}$ (proton) needs to be proposed and forming this free proton would require a great deal of energy, as well as an explanation for why the bond simply falls apart.

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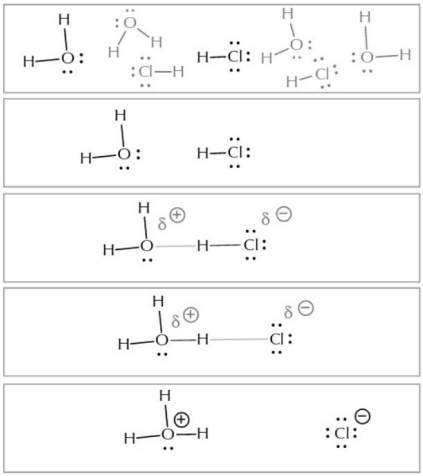
The third option, with both bonding changes happening at the same time, is the best proposal here because, on average, the hydrogen atom is maintaining its duet. The old 2-electron HCl bond is breaking as the new 2-electron OH bond is forming, and this is implied by a drawing in which both curved arrows appear together. In a physical sense, we imagine the bonding changes occurring as the result of a collision, where the oxygen atom of water careens into the hydrogen atom of HCl, contributing the energy required for the HCl bond to break and providing a rationale for how and why the HCl bond can break. A visualization for the collision, using a snapshot sequence of static images, is shown in Figure 0158.

Figure 0158

A sequence of static images that illustrate the option 3 mechanism of water plus HCl.



among many molecules in the solution, one of oxygen atoms moves to collide with the hydrogen atom of an HCl, along a trajectory that is along the line of the HCl bond

isolating the view to those two molecules, the oxygen atom moves closer to the hydrogen atom

the oxygen atom collides with the hydrogen atom: a new OH bond forms as the HCl bond breaks; electron flow results in weak partial charges on the atoms that will end up charged

the forming OH bond strengthens as the oxygen draws closer, as the chlorine atom is being released; the formal charges are increasing in intensity as the bonding changes

the new OH bond has formed, along with the positive formal charge, and the chlorine atom has departed as a chloride ion

One of the distinctive differences between options 2 and 3 is that a different number of mechanistic steps are being described. Option 2 is an example of a 2-step mechanism (step 1: the HCl bond breaks and forms intermediate structures; step 2: the intermediate structures react to form the new OH bond), while option 3 is a 1-step mechanism (no intermediate structures, the bonding changes are proposed to take place at the same time). Some key experiments that are used to gather mechanistic information are to assess whether a reaction takes place in one or more steps, and to identify intermediate structures. In fact, the experimental evidence supports option 3 for this reaction.

Drawing the sequence of curved arrows. As described earlier, each curved arrow illustrates the implied reorganization of an electron pair, from the place it originates and pointing to the destination. When there are more than two arrows needed to describe a mechanism on the same set of structures, such as in option 3, above, the information about which arrow was drawn first is obviously lost when both are shown together. And yet, there is an explicit electron flow that is implied by the multi-arrow mechanism (Figure 0159), because there is an ultimate electron source as well as an ultimate electron destination. Consequently, experienced organic chemists have adopted a nearly subconscious bias to lay the curved arrows down, when they draw them, according to the implied electron flow. There is no question that organic chemists would agree that there is a "first arrow" and a "second arrow" when they draw this mechanism.

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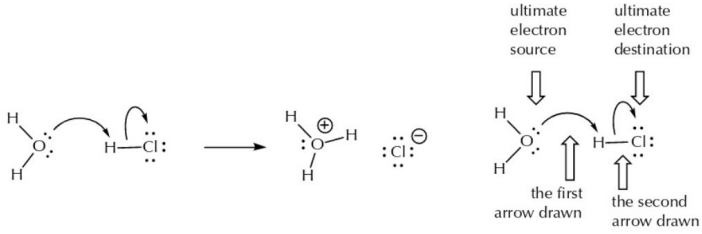
Figure 0159

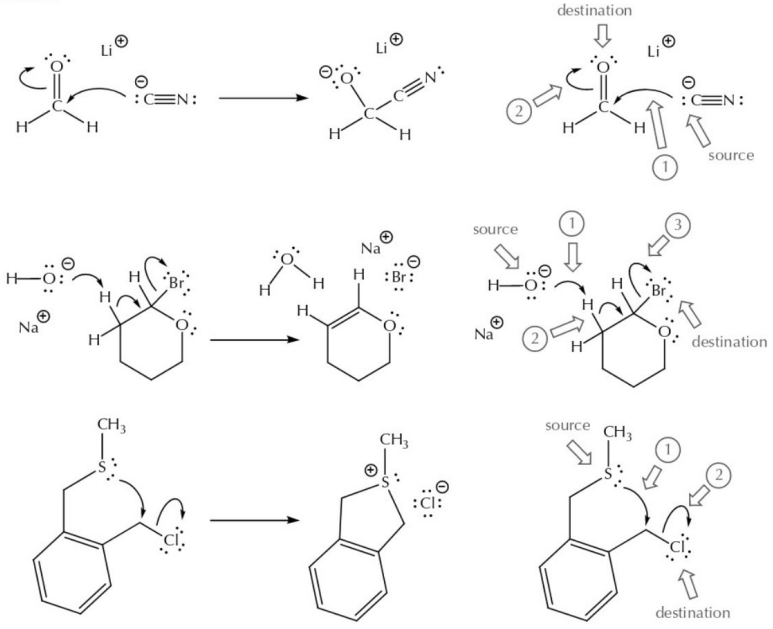
The implied electron flow, and arrow-drawing order, for the option 3 mechanism of water plus HCl.



Several examples of multi-arrow mechanisms that are known to take place in one step are shown in Figure 0160, including an indication of the electron source, the electron destination, and the most likely order that an expert would draw the curved arrows.

Figure 0160

The implied electron flow, and arrow-drawing order, for some representative one-step mechanisms.



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PRACTICE QUESTIONS

1.25 Provide the complete Lewis structures (lines for covalent bonds, nonbonding electron pairs, formal charges) for the compounds whose condensed molecular formulas are shown. All atoms are closed shell. Ionic compounds should be shown as separated ions.

(a) diazene HNNH

(b) ammonium fluoride NH_4F

(c) methylene chloride CH_2Cl_2

(d) magnesium cyanide $Mg(CN)_2$

(e) tetramethylammonium hydroxide $(CH_3)_4NOH$

(f) acetaldehyde oxime CH_3CHNOH

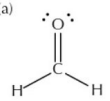
(g) acetaldehyde oxime CH_3CHOO

(h) acetic acid CH_3CO_2H

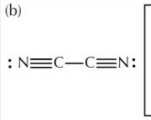
(i) butyllithium $CH_3CH_2CH_2CH_2Li$

1.26 The following molecules are shown with their molecular geometries (they are all linear or planar). Provide the direction of each anticipated bond dipoles adjacent to the bond itself and then also the overall direction of the molecular dipole moment, if expected, in the adjacent space (write "none" if no molecular dipole moment is expected).

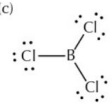
(a)



(b)

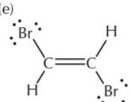


(c)

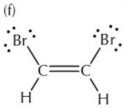


(d)

(e)



(f)



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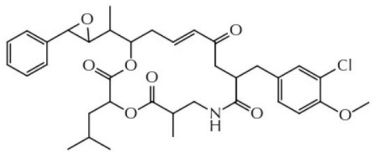
1.27 How many units of unsaturation are represented by the following molecular formulas?

(a) C_3H_9N	(b) $C_{15}H_{24}$	(c) N_2H_2	(d) $C_6H_{15}B$
(e) $C_{17}H_{19}N_3$	(f) $C_{21}H_{36}N_8O_6$	(g) $C_{42}H_{68}N_6O_6S$	(h) $C_{11}H_5Cl_4N_3O_3$

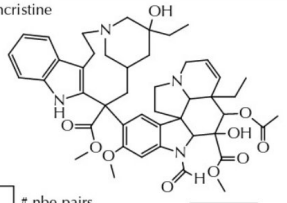
1.28 Many potential anticancer agents are extracted from natural sources, such as marine organisms. The following four naturally occuring molecules have been examined for their antitumor activity. Try counting the number of hydrogen atoms by inspection of the structures, then use the units of unsaturation to calculate the number of hydrogen atoms present, and see how your numbers compare, as well as the relative ease of the two methods. Nonbonding electron (nbe) pairs have been excluded as an additional counting exercise.

(a) cryptophycin A



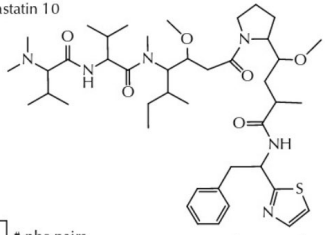
nbe pairs
units of unsaturation
C
H

(b) vincristine



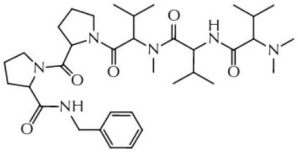
nbe pairs
units of unsaturation
C
H

(c) dolastatin 10



nbe pairs
units of unsaturation
C
H

(d) cemotidin



nbe pairs
units of unsaturation
C
H

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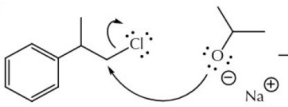
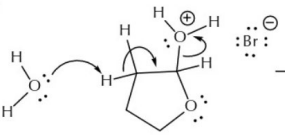
1.29 Provide the structures implied by these curved arrows. Equations should balance in atoms and charges, and account for nonbonding electrons. All atoms are closed shell.

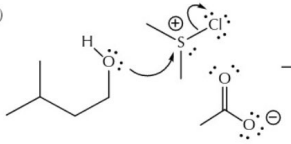
(a)



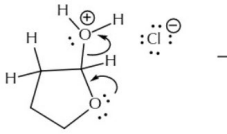
(b)



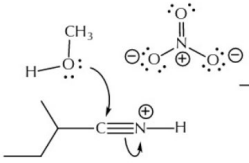
(c)



(d)



(e)



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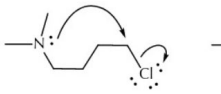

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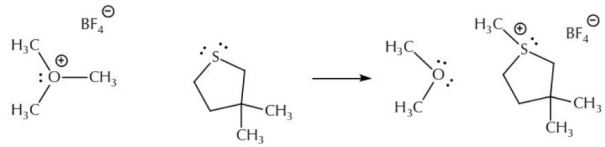
1.30 Provide the curved arrow mechanism implied by these chemical equations, assuming that all of the bonding changes occur in a single step.

(a)



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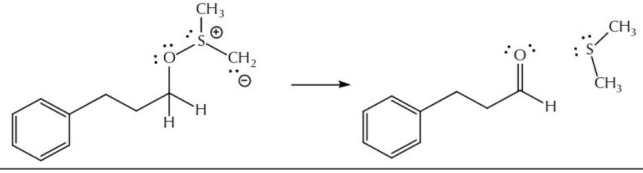

(c)

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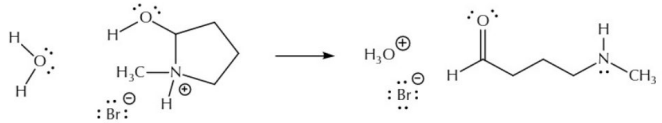
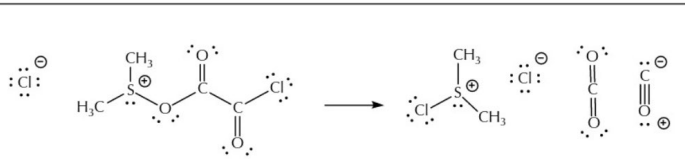


(e)



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Reflections About Science: We Invent the World

The story about acetic and succinic acids from the 1830 text by Thomas Thomson is an important reminder about science. Science is a human activity that derives in great part from common sense combined with specialized knowledge. Chemists did not "discover" molecular structure because they were looking for it, but "invented" molecular structure to solve a problem. Direct experimental evidence for molecular structure would not be available for about 100 years.

Chemists, and anyone who needs or uses evidence to make their case, are anchored to the real world, not only in the requirement for making observations and reporting them as truthfully as possible (something that the 20th century physicist Richard Feynman called "utter honesty"), but also in understanding their own role (as humans) and the potential human bias in making observations in the first place.

One of the most significant ideas to emerge in the 20th century comes from Werner Heisenberg (1932 Nobel Laureate). In a terrific book he wrote for the public, Heisenberg dispels the idea that scientists can stand apart from the world objectively and dispassionately (what he calls, interestingly enough, "a scientific view in the true sense of the word"). Instead, "method and object can no longer be separated."

> Modern man confronts only himself… The scientific method of analyzing, explaining and classifying has become conscious of its limitations, which arise out of the fact that by its intervention science alters and refashions the object of investigation. In other words, method and object can no longer be separated. The scientific world-view has ceased to be a scientific view in the true sense of the word.
>
> W Heisenberg (Pomerans translation), *The Physicist's Conception of Nature*, London: Hutchinson, **1958**, 29.

Scientists, like most people, are often loath to change their minds, and so another reminder that science also operates within a social and societal framework populated by people, including all of their strengths and weaknesses.

In the early 20th century, quantum mechanics gave rise to many fundamentally new ideas and experimental techniques that revolutionized chemistry and society. The medical visualization technique called MRI (Magnetic Resonance Imaging) is derived directly from one of the most important techniques we have for gathering evidence about organic molecular structure, called NMR (Nuclear Magnetic Resonance). The initial reason for running the NMR experiment was not about determining molecular structure, however, but rather a way to test one of the predictions from quantum mechanics.

And yet, for its proven strengths, there were many scientists who vehemently rejected aspects of quantum mechanics. So much so that Max Planck, a pioneer in quantum mechanics and 1918 Nobel Laureate, wrote in frustration:

> A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it.
>
> M Planck (Gaynor translation), *Scientific Autobiography and Other Papers*, New York: Philosophical Library, **1949**, 33 (often paraphrased as 'science only makes progress funeral by funeral').

Despite Planck's impatient cynicism, the human drive to solve the significant problems of our time, whatever time it is, captures the imagination and creativity of scientists. Today, chemists around the world are making

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progress on energy storage, medicine, sustainability of earth's resources, preservation of the global environment, and so on. The 1988 Nobelist, Gertrude B. Elion, spoke often of the human element in scientific pursuits.

> It is important to go into work you would like to do. Then it doesn't seem like work. You sometimes feel it's almost too good to be true that someone will pay you for enjoying yourself. I've been very fortunate that my work led to useful drugs for a variety of serious illnesses. The thrill of seeing people get well who might otherwise have died of diseases like leukemia, kidney failure, and herpes virus encephalitis cannot be described in words. The Nobel Prize was only the icing on the cake. There may be those who try to deter you and discourage you along the way. But keep your eye on the goal. And in the words of Admiral Farragut, "Damn the torpedoes, full speed ahead!"
>
> As quoted by ME Avery, in "Gertrude B. Elion" *National Academy Memoires*, **2000**, *78*, 16.

As exemplified by this first chapter, I think that a sense of history can provide a deeper and more authentic context for understanding science because science is carried out by regular people using a bit of specialized training, but still rooted in many common-sense ideas and practices that drive them to explore some small part of the world.

Communication is a key part of science (and everything else for that matter). All of the invention and discovery in the world cannot help anyone if a person cannot clearly express their ideas. And for this reason, the invention of new words, along with the adaption of existing words, is another theme that you will see in this text. I want you to understand that these so-called scientific terms are so often invented to communicate something useful about molecular structure and/or reactivity, so it can benefit your learning, quite directly, when you can know what the inventor of a word was trying to tell you.

As a student learning organic chemistry for the first time, one of the things that I appreciated the most about the subject was the feeling that I was being let in on a shared secret. The study of organic chemistry lets you into a part of the world where so many things that you might have previously encountered, but never quite thought you could understand, end up making nearly intuitive sense.

In her 2018 Nobel Banquet Address, Frances Arnold reminds all of us that, in science, the sky is indeed the limit, but that its potential power is accompanied by moral responsibility.

> We … create molecules for the common good. We share deep admiration for evolution, a force of Nature that has led to the finest chemistry of all time, and to all living things on this planet. The fuel for evolution is diversity, with natural selection leading to continuous adaptations and improvements in Nature's handiwork. Organisms (and organizations) without this diversity are doomed to extinction in a rapidly changing world.
>
> Yet Nature has explored only a tiny fraction of the life and life's molecules that are possible. With evolution in our hands, with the ability to set genetic diversity and to tailor the forces of selection, we can now explore paths that Nature has left unexplored. We can also explore paths that Nature will never explore: we can select living organisms and their chemistries for our benefit—to create new sources of energy, to fix the carbon in our atmosphere, to cure disease or to make us younger. Or we can make new weapons of terror or of state control … which shall it be?
>
> Frances H. Arnold—Banquet speech (18 December 2018). NobelPrize.org. https://www.nobelprize.org/prizes/chemistry/2018/arnold/speech

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As you develop your molecular, mechanistic, and common (chemical) sense, then even after one year of study, some interesting things about the world are simply revealed to you. Just a few of the mysteries that will be unraveled as you learn organic chemistry for the first time include:

Why it is that when a person has consumed wood alcohol (methanol) that the best treatment is an intravenous dose of grain alcohol (ethanol)?

Why was azidothymidine (AZT), which proved to be effective in 1985 at inhibiting the replication of the HIV virus, a molecule that had been deliberately designed and prepared in 1964, 20 years before AIDS was even defined?

How can changing a meager handful of atoms, [-CH(CH$_3$)$_2$] instead of [-CH$_2$CO$_2$H], from among the thousands that make up a hemoglobin molecule, lead to a form of anemia?

Starch and cellulose are one of many examples of chemically identical molecules that are yet remarkably different in the way your body reacts and interacts. What is this difference, and in the case of starch and cellulose, how does the explanation apply to people who have lactose intolerance?

How do antibiotics function and what is the actual meaning of the idea of "antibiotic resistance"?

Welcome, again, to your study of organic chemistry.

Summary

From a prior study of basic chemistry, organic chemistry students should be comfortable with the distinction between atoms, ions, and molecules, including the assignment of formal charge to an atom. An understanding of electronegativity and its effect on atomic properties in rows and columns of the periodic table is required. A descriptive idea about the difference between covalent and ionic compounds is important, including the usual valence/bonding state of organic main group elements.

Multiple criteria are used to assess the relative stability of organic molecular structures. These criteria are generally ranked as (a) closed shell atoms are better than open shell atoms, (b) uncharged atoms are better than charged atoms, (c) placement of negative charge on a more electronegative atom is better than on a more electropositive one, and vice versa, and (d) opposite charges in greater proximity are better than being separated, and vice versa for like charges.

Molecular formulas not only provide a useful way to keep track of atoms in a balanced equation, but also, historically, resulted in many of the terms we use to describe or classify reactions today (such as "addition"). Any given molecular formula generally represents a large collection of structural isomers. An understanding about units of unsaturation creates a useful cross-check for the accuracy of any created isomers as well as for counting (by calculation) the number of hydrogen atoms in the structure when the molecular formula is not provided.

Representational drawings for organic molecular structures include Lewis structures, line abbreviation and condensed formula forms. These types of drawings are often combined, depending on what needs to be communicated.

A reaction mechanism is the description of the stepwise process on bonding changes that link the structures of the starting materials to the products. The curved arrow notation is used to tell the story of the bonding changes, representing an electron flow as new bonds form and old bonds are broken.

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CHAPTER QUESTIONS

1.31 There are seven structural isomers (a-g) for $C_4H_{10}O$ with all closed shell and uncharged atoms. Draw them using line abbreviation drawings. Include the nonbonding electron pairs.

(a)	(b)	(c)
(d)	(e)	(f)
(g)	for this last one you drew, (g), the oxygen atom uses one of its nbe to form a new bond with the hydrogen atom of HCl, while simultaneously, the HCl bond breaks to give chloride ion. Draw that outcome of that reaction. (g) $\xrightarrow{HCl}$	

1.32 Which of the following compounds have connectivities with all singly bonded atoms and no rings in their structural formulas (i.e., saturated compounds)?

- ☐ (a) C_2F_4 (the monomer tetrafluoroethene, used to make Teflon)
- ☐ (b) $C_{14}H_9Cl_5$ (the formula for DDT, an insecticide)
- ☐ (c) $C_2HBrClF_3$ (the formula for halothane, an anesthetic)
- ☐ (d) $C_{10}H_{16}$ (the formula for adamantane, a molecule that resembles diamond in its structure)
- ☐ (e) $C_{20}H_{42}$ (the formula for icosane, found in Vaseline)
- ☐ (f) C_2H_3Cl (the formula for vinyl chloride, used to make plastics)
- ☐ (g) $CHCl_3$ (the formula for chloroform, used in old movies to knock people out)
- ☐ (h) C_4H_7Cl (the formula for methallyl chloride, a fumigant)

1.33 Three of the molecules listed in question 1.32 have only one possible connectivity in which all of the atoms are closed shell and uncharged. Which ones are they? Draw them.

letter ☐	letter ☐	letter ☐

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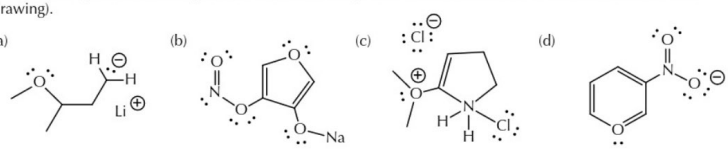
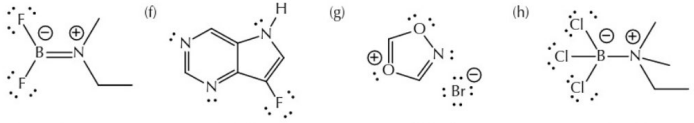
1.34 Four of the following molecular structural drawings have errors in them. If all of the atoms have closed shell electron configurations, identify and correct the drawings with errors (there can be more than one error in a drawing).

(a) (b) (c) (d)



(e) (f) (g) (h)



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1.35 Carbon monoxide, CO, has a much smaller dipole moment than expected (0.112 D, compared with, for example, H_2CO, which has a dipole moment of 1.56 D). This observation has puzzled chemists and led to much debate about the nature of the bonding in the molecule. Draw the structures for both CO and H_2CO, both of which have all closed shell atoms, and suggest why the carbon monoxide dipole moment is smaller than expected.

H_2CO CO

1.36 Carbon monoxide, CO (see question 1.35), is observed to react in a 1:1 stoichiometric ratio with borane (BH_3). Draw the Lewis structures for CO and BH_3, predict the reaction product, and show the curved arrow mechanism.

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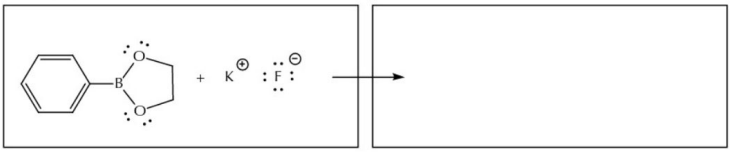
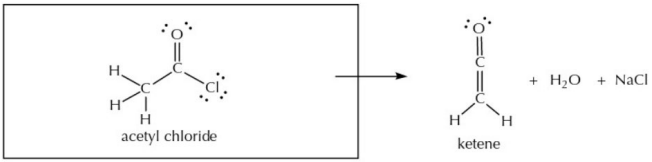
1.37 Predict the structure of the product in the following chemical reaction (make sure the equation is balanced), as well as the curved arrow mechanism.

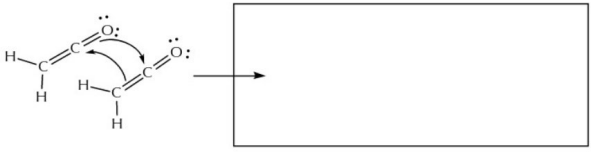


1.38 Ketene is one of the C_3H_2O structural isomers. A condensed formula for ketene is $H_2C{=}C{=}O$. Ketene can be formed by the reaction between acetyl chloride and sodium hydroxide (below).

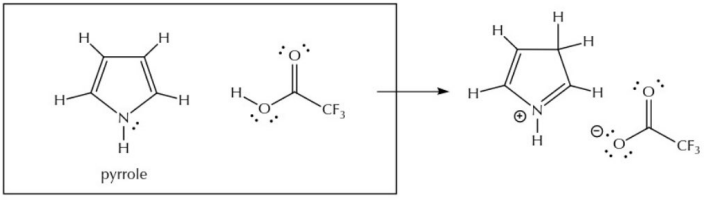
(a) Add sodium hydroxide (NaOH) acetyl chloride and provide the curved arrow mechanism for the formation of ketene, which takes place in one step.



(b) Ketene can react with itself in what is called a dimerization reaction. The following shows the mechanism for the dimerization of two ketenes. Draw the structure of ketene dimer.



1.39 Pyrroles are common heterocyclic rings in biological molecules, including the porphyrins of heme, in hemoglobin, the chlorins and bacteriochlorins of chlorophyll, and the corrin ring of vitamin B12. One fundamental reaction of pyrroles is shown here. Provide the curved arrows for the following one-step mechanism.



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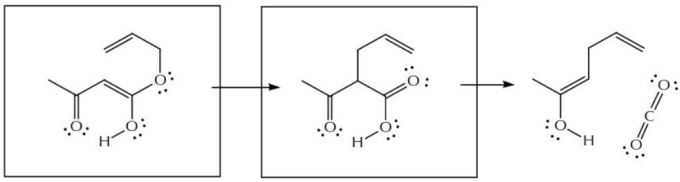
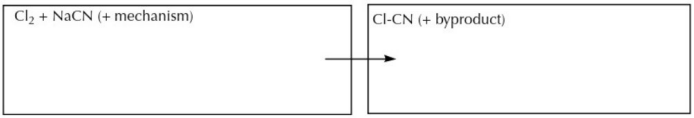
1.40 The Carroll rearrangement is a two-step transformation. Using the curved arrow notation, with the minimum number of arrows necessary to depict the movement of electrons, provide the mechanism for the following.

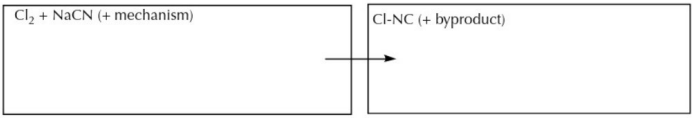


1.41 Cyanogen chloride is a low boiling colorless gas whose connectivity is Cl-CN. This compund is quite toxic, and was considered for use in chemical warfare because of its ability to cause injury to the eyes, nose, throat, and lungs. Even relatively small exposures can be fatal.

(a) Cyanogen chloride is prepared by the reaction between chlorine gas (Cl_2) and sodium cyanide (NaCN). In the space below, draw (i) the Lewis structures for Cl_2 and NaCN, (ii) using the curved-arrow notation, the arrows that describe the 1-step mechanism for the reaction that results in cyanogen chloride (Cl-CN), and (iii) the Lewis structure for cyanogen chloride. Include nonbonding electron pairs, formal charges, and the balanced equation.



(b) When the reaction to prepare cyanogen chloride is carried out, an isomeric by-product called an isocyanide is formed. The connectivity for the isocyanide is Cl-NC. Provide the complete reaction, as in part (a), for the mechanism of formation of Cl-NC.



(c) When cyanogen chloride (Cl-CN) is heated under certain experimental conditions, a new, stable substance forms in a trimerization reaction. Some of the properties of this new compound are given below. Based on these data, propose a complete Lewis structure for the cyanogen chloride trimer, whose molecular formula is $C_3Cl_3N_3$.

3 Cl-CN ⟶ $C_3Cl_3N_3$

all atoms closed shell
all atoms uncharged
molecular dipole moment = 0 D

hint: how many units of unsaturation in the trimer?

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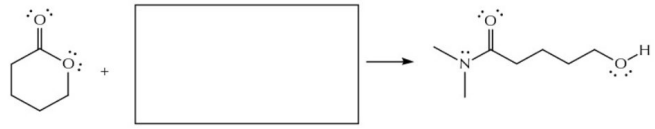
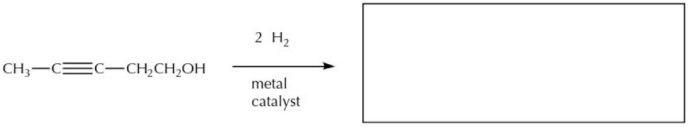
1.42 Complete the following reactions by providing the structure of the missing reagent or product. The equations should be balanced, and all of the structures have closed shell atoms.

(a)

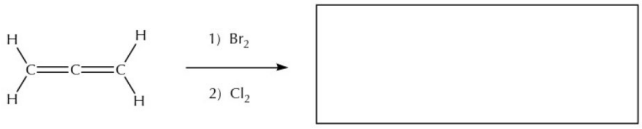


(b) an addition reaction



(c)

(d) a sequence of 2 addition reactions: 1 equivalent of Br_2 followed by 1 equivalent of Cl_2



1.43 Methyl azide (CH_3N_3) is a neutral molecule with the H_3CNNN connectivity. There are two different Lewis structures that can be drawn for methyl azide that have all closed shell atoms.

(a) How many units of unsaturation are there in CH_3N_3?

(b) Draw the two Lewis structures for methyl azide, including nonbonding electron pairs and formal charges.

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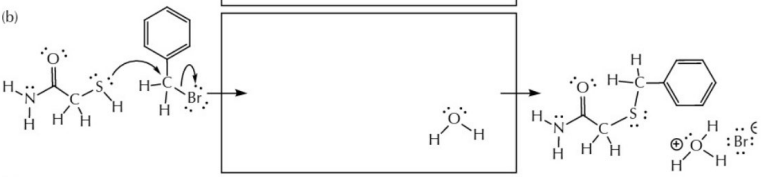
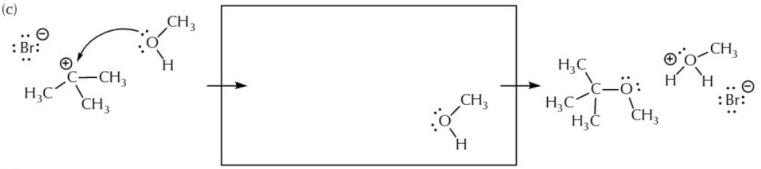
1.44 For each of the following examples, draw the structure implied by the curved arrows. In that answer space, there is another reagent shown. Using the structure you have drawn and the provided reagent, show the curved arrows for the single step needed to transform that structure into the final products.

(a)

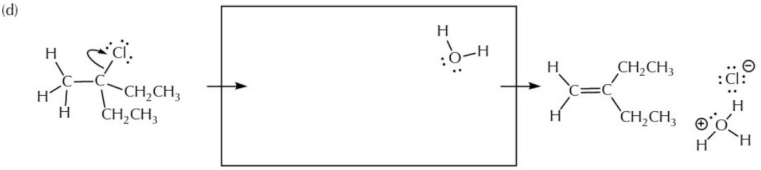
(b)



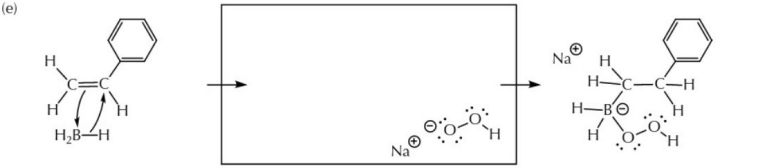
(c)



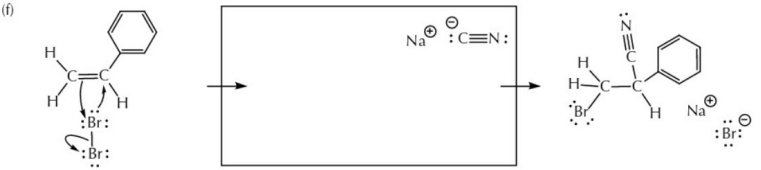
(d)



(e)



(f)



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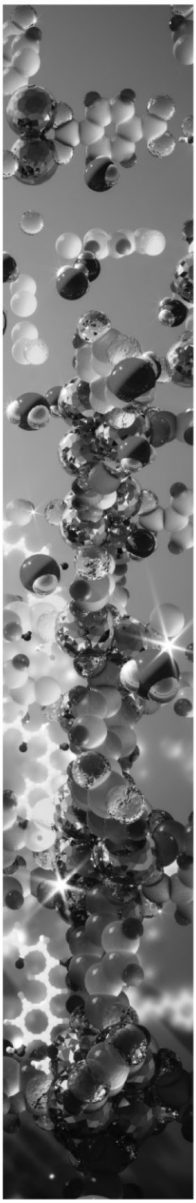

CHAPTER 2

Organic Molecular Structure and Properties

Setting the Stage: Learning New Things and Learning to Explain Them

2.1 Delocalized Electrons and the Limits of Valence Bond Molecular Structures

- A. The Relative Reactivity of Polar Covalent Bonds
- B. Using Delocalized Electrons to Explain Structure and Reactivity
- C. Using Resonance Contributors to Represent a Molecular Structure with Delocalized Electrons
- D. Predicting Delocalizable Electrons, Drawing Resonance Contributors, and Evaluating Resonance Contributors

PRACTICE QUESTIONS

2.2 Bonding Models That Account for Molecular Structure and Properties

- A. Molecular Geometry Centered at Atoms: The VSEPR Model
- B. The Quantum Mechanics Conundrum
- C. Molecular Geometry Centered at Atoms: The Hybridization Model
- D. A Unified Picture for VSEPR, Hybridization, and Delocalized Electron Structures

PRACTICE QUESTIONS

2.3 Bonded and Nonbonded Structure and Properties

- A. Bond Lengths
- B. Van der Waals Interactions: London Dispersion Forces and Induced Dipoles
- C. Van der Waals Interactions: Permanent Dipole-Dipole
- D. Hydrogen Bonding

PRACTICE QUESTIONS

Reflections About Science: Method and Object Cannot Be Separated

Summary

CHAPTER QUESTIONS

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CHAPTER 2

Organic Molecular Structure and Properties

Setting the Stage: Learning New Things and Learning to Explain Them

Chapter 1 was intended to level the playing field for students, taking in account the variable prior experiences with chemistry and revisiting mostly familiar territory as seen through the lens of learning organic chemistry. The curved arrow convention was likely new for most students, but it is not really a topic in chemical science as much as it is a bookkeeping and communication tool that we will be putting to constant use.

Chapters 2 and 3 move rapidly to learning new things about chemistry, and that also means changing, or transforming, your worldview about science. "Transformation" is a lovely term to represent change because it is commonly used in chemistry (the transformation of a starting material to its product), and because it implicitly acknowledges that where you are starting from matters. For learning, that means your prior knowledge and experience form the foundation on which you can build new knowledge.

A textbook commonly puts its essay on learning at the very beginning, sometimes before the Table of Contents, because an author wants to try and give you that advice from the outset. I decided to hold off until chapter 2, to wait until you might be more receptive to getting advice after completing some of those familiar topics in chapter 1, and after looking at them in what might be some new and unfamiliar ways.

In other words: *Now that I have your attention…* I want to talk with you about the big topics in learning that are driving my decisions as a teacher of organic chemistry.

In 2012, a pair of educational psychologists reviewed decades of work about learning and assembled it into a useful, three-part design for teaching and learning. They called their design "transformational teaching."

> We believe that to be transformational in nature, teaching must enhance students' mastery of course concepts, their learning-related skills, and their disposition toward learning.
>
> G.M. Slavich, P.G. Zimbardo, Transformational teaching: Theoretical underpinnings, basic principles, and core methods, *Educational Psychology Review*, **2012**, *24*(4), 569.

In this essay, I will recommend how these three design principles (mastery of course concepts, learning-related skills, and disposition toward learning) might transform the way you think about learning.

Mastery of Course Concepts

Mastery of concepts is not the same as memorizing a list of factoids. It does not make memorization bad; it just makes that sort of learning extremely limited and not transformative. You can memorize and repeat things and have no idea whatsoever what you are talking about. I use learning multiplication as an example of this. You can code the symbolism of "2 x 5" and have a stimulus response to it ("10") and have no clue at all what the process is. As long as an item appears on your memorized list, you are OK, and you can reply. But the moment the item is not on the list and requires you to understand multiplication ("3.5 x 8.25") you are lost to answer the question, or you completely externalize it by punching it out on your phone's calculator.

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Plenty of things cannot be learned this way. You cannot learn to drive a car, ride a bike, play a piano, act in a play, score a goal, or create a painting, by reading a book and repeating a bunch of memorized facts. For so many things you learn outside of school, you naturally understand that actual performance of your understanding matters as much as your knowledge of facts and your ability to recite, recall, and repeat them. All of the facts might be useful, such as the rules of a game, but your performance is related to practice, inevitably from making and correcting errors, and benefits from asking the types of questions that only a person who has started something and gained experience can possibly pose. You seek out those who are more skilled than you are, and you are motivated to learn from them because you are curious.

As a student (and I still am and I always will be), I admit to being chronically curious. In my life, I have not put any value judgment on what I was interested in learning, because you just never know where it leads or when the information might be useful. Or it might just be a story you tell because it is an intrinsically or broadly interesting insight into the human condition.

Learning everything, including an academic subject, shares all of the hallmarks of learning art or sports or other games, but—quite unfortunately—school subjects are too often presented and/or perceived as the memorization of facts you are handed (being given some marbles), with test-taking as the ability to recall and return the facts (returning the marbles), with no actual thinking, learning, or transformation.

As an educator, it frustrates me that courses are organized that way, and more so because students LEARN that this is all that is expected. And I see so many students who are so clearly capable of learning new things and developing expertise, and then turn around and treat their academic work with dull-eyed indifference… and yes, because sometimes the entire enterprise is being treated with dull-eyed indifference, but that should never prevent you from being curious and living up to your potential.

Mastery of concepts means having information and knowing how to use it correctly and knowing that when you face new and unfamiliar information, you can think through how to make sense of it, how to make analogies from what you know, and how to apply the concepts to the solution of a new problem.

> *I am going to give, here, my single best prescription for how to motivate you to master concepts. In my experience, the greatest indicator that you have learned something is your ability to teach it to others.*

When you can take an understanding that you have and can effectively share it with others, you are not only thinking about the subject, you are thinking about understanding where that other person is starting from and sorting through as many different pathways as you can to make the link between what you know and what they know.

Your understanding of any topic is necessarily incomplete and might have errors that escaped your detection; but when you and others are willing to talk and debate and defend your ideas and understand that you will also necessarily change your mind about something you thought was true, you are in a situation in which you experience transformation. If you work with others and you do not prepare, you are not a responsible partner. If you only listen and never participate in the debate, you are not a responsible partner.

And now, the real secret that ought to be told from the start of schooling: testing, whether it is an exam or a paper or a presentation is, at its core, a teaching event. Testing is simply a role reversal between students and teachers; that is, someone is putting you in a situation where you are explaining what you know. Even an examination is the same as a peer who comes to you and asks, "can you help me go through how to do this?"

This is why you are encouraged to work with peers, and particularly to be the one sitting with a pencil and blank piece of paper, or the one standing at the board and leading the discussion. The thought process,

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of taking what you know and transforming it into a coherent explanation, is wholly different than learning it for yourself, and it is exactly what you must do for an examination. So, you have a simple, simple choice:

Are you willing to practice explaining what you are learning before the examination, and sorting through those undetected errors before the test, or do you wait until exactly the worst moment to practice explaining things: doing it for the first time at the examination?

I have made my point; but let me follow up with one related idea before I move on to the second attribute of transformational teaching and learning. This idea is compelling and there is strong research to support it:

> *When you are aware of the future requirement to explain (teach) something, you will actually learn it better in first place, because anticipating and rehearsing teaching will be a part of your learning.*

Imagine I recommend that you read a news article on the internet. You can imagine you are reading it for personal knowledge, and you can imagine capturing the meaning.

Now let me add this: I recommend that same article, but I tell you that you need to make a presentation and lead a critical discussion about it tomorrow.

My question to you is simple and rhetorical, because I know the answer: will you read the article differently in the second situation than in the first? The answer, universally, is yes. Keep that in mind, because everything you do in school that has an exam, paper, or presentation is the second situation, not the first one. When you are consciously aware of the future need to explain what you know, you learn it better. This is a simple, experimentally affirmed fact.

And the only choice you have, like it or not, is when you make your errors. If you do not practice your explanatory skills before an exam, you are leaving it for what is arguably exactly the wrong time: at the exam.

Mastery of course concepts is transformative in your learning because you will have changed yourself into a person who can explain what you have learned to others.

Learning-Related Skills

In their transformational teaching principles, George Slavich and Phil Zimbardo claim that a person who has been educated properly will experience "positive, learning-related attitudes, values, and beliefs."

This phrase is a fantastic reminder that so much that is intended to be learned does not appear explicitly on the syllabus, in the textbook, or on the exams… but does appear implicitly.

When I think about organic chemistry, I am not only thinking about the facts. I am thinking critically and with scientific skepticism about the experiments, and what the evidence does or does not support in terms of conclusions. I am thinking about how to tie together what I know and create a coherent explanation for others to follow (including in this book). I am thinking about the history of the ideas and what it tells me; the use of language and what it tells me; how the topics relate to other concerns, such as health and nutrition.

All of these topics are "learning-related" but at no point in my course do I stop and say, "today our lesson is scientific skepticism." Instead, scientific skepticism is embedded in my understanding of my subject, and every time I open my mouth, things like how science operates are informing how I talk about science and the choices I make in teaching.

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Sometimes I do pause and point these things out, but most of the time I am displaying them by example. By naturally displaying my thinking processes, I expect that these are habits of mind that will rub off on students who see, hear, or read my ideas.

Learning-related attitudes, values, and beliefs are transformative in your learning because you will develop abilities such as scientific skepticism, clarity of making arguments, improved skills for writing and speaking clearly, making analogies, and so on. Your interaction with experts, and why you should want to interact with experts, is where these benefits are derived.

Disposition Toward Learning

Every learning situation you are in ought to transform you into a person who can learn better, in that you learn something new about learning. In designing a course, I am deeply committed to creating an environment that enables students to try new learning strategies that I think are valuable to learning the subject. And in designing this text, I had the same goal. But a text cannot carry the solitary burden for your learning; no single learning tool can do that.

If learning is a process of building knowledge, then the learning resources available to you are the tools you use for its construction. Tools are diverse, serving different needs and accomplishing different outcomes, and they serve different people in different ways.

Tools are also neutral in that it is just as easy to use them badly as it is to use them well.

Standard learning resources include class meetings, a textbook, question sets, answer keys, study groups, organized discussion sessions, office hours, internet lessons, practice sets with feedback, and even quality alone time and haphazard meetings at a coffee shop.

In general, you have so many different learning resources available to you that you need to make an informed choice about which combination is best for you. We have been studying the use and usefulness of how students engage with learning resources for more than 15 years, and we have two important observations to share about learning how to learn.

There are no magic bullet combinations. While the most academically successful students end up identifying a combination of about 6 to 7 resources that they learn to use effectively, there is absolutely no particular combination of resources that is more effective than any other. We think of this as a trip to a large and varied food buffet, where you are charged with coming back to the table with a well-balanced and nutritious meal. There is not one best tray of food that solves this problem; there are many, and what is palatable and delicious to one person is not automatically the same to another. The take-away here is terribly important: you might see a person who is doing well in a class and immediately want to know from them, "what are you doing?" Their answer might be useful to you, but it also might be completely irrelevant to you. There are no magic bullets.

Transformation requires change, and change requires exploration. Intellectual stubbornness and the resistance to change, as a matter of basic habit, is not conducive to learning. Years ago, at a meeting I attended, the literary critic and philosopher Wayne Booth provided his definition of a truly critical thinker and it sticks with me to this day: a truly critical thinker is a person who, in the face of evidence and argument, can change their mind about something important to them at least once a day. If you never change your mind about important things, you think you have the right answer to everything already, and this is irrational.

Experimentally, we know that students who land at about 6 to 7 useful learning resources do the best in our classes. To get there, they need to refine what they are doing to improve and adapt them to the course,

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they need to try out some new resources, and they need to identify what is not working and either change their approach or reject them and try something new.

We have observed, on a large scale, that students see increased exam performance when (a) they find something that is useful and then stick with it (we call this EXPLOITING the resource), (b) they stop using something that was deemed not useful (we call this PRUNING the resource), and (c) they try something new (we call this EXPLORING the resource)—in other words, taking a critical look at what you are doing and making the changes needed to do better turn out to correlate with achievement.

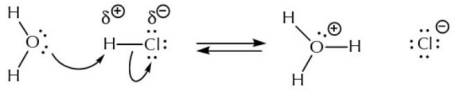
This disposition towards learning is called self-regulation: to be able to match yourself in a strategic way with the learning strategies that work best for you in terms of actual outcome, not because others are doing them, not because you are reticent to change, and not because you believe you are predisposed to only a certain way to learn or that there are subjects about which you cannot achieve. Learning how to learn, and expanding your toolbox for learning, is intrinsically good and a transformative experience if you allow it to be.

2.1 Delocalized Electrons and the Limits of Valence Bond Molecular Structures

A. The Relative Reactivity of Polar Covalent Bonds

A great deal of organic molecular reactivity is centered on changes in polar covalent bonds. Nonbonding electron pairs are a source of electrons for making new bonds, and the polarized nature of the polar covalent bond means that it is already on its way to breaking in a heterolytic manner, where the electron pair comprising the bond ends up with one of the atoms. The reaction between the polar covalent bond in HCl and the nonbonding electron pair from the oxygen atom in the water molecule is a familiar example (Figure 0201).

Figure 0201
Reaction with polar covalent bond.



A typical reaction between an atom with the nbe pair and a molecule with a polar covalent bond.

As you might recall from your study of introductory chemistry, this particular chemical reaction (between water and pure, gaseous hydrochloric acid) quite favorably lies towards the right-hand side of the equation and the formation of the ionic hydronium chloride product.

Quantitatively, the extent of the reaction can be expressed as a percent yield (the reaction might proceed to give 100% formation of the products, or less than that if some of the starting material is unreacted, or if there are byproducts, or if the reaction is an equilibrium in which the ratio of starting materials to products becomes a constant value). Another way to express the extent of a reaction is with the equilibrium constant (Figure 0202): the ratio of the concentration of the products to the reactants.

Figure 0202
Defining the equilibrium constant (in general).

$$K_{EQUILIBRIUM} \text{ (or } K_{EQ}) = \frac{\text{concentration of products}}{\text{concentration of reactants}}$$

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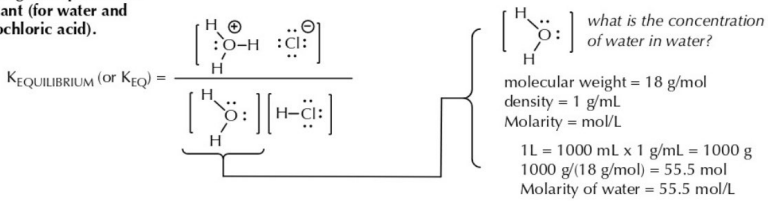
For reversible reactions, in which the transformation can run in both directions, equilibrium is the point at which the rate of the forward reaction is the same as the rate of the reverse reaction, and so the ratio of products to starting materials hits a fixed value (even though both reactions are still operating).

At equilibrium, if the concentration of products is greater than the reactants (i.e., the numerator is greater than the denominator), then K_{EQ} is greater than 1. If the two concentrations are equal, then K_{EQ} is equal to 1. If the concentration of reactants is greater, then K_{EQ} is a fraction between 0 and 1.

The equilibrium constant for the reaction between water and hydrochloric acid can be expressed specifically (Figure 0203).

Figure 0203

Defining the equalibrium constant (for water and hydrochloric acid).


K EQUILIBRIUM (or K EQ) =
what is the concentration of water in water?
molecular weight = 18 g/mol
density = 1 g/mL
Molarity = mol/L
1L = 1000 mL x 1 g/mL = 1000 g
1000 g/(18 g/mol) = 55.5 mol
Molarity of water = 55.5 mol/L

Experimentally, if a 1:1 mixture of water and HCl are combined in a neutral solvent, the K_{EQ} is about 10^8, a large number which means, in any practical sense, that you are only going to detect the hydronium chloride product. And when the solvent is water, this will shift the equilibrium even further to the right, according to the Le Châtelier Principle, because water appears in the equation. In practice, the amount of water is much greater than the amount of HCl, and the concentration of water in this equation is effectively a constant. Figure 0203 also includes a reminder about the mathematics behind the answer to the question: what is the concentration of water in water, in units of molarity (mol/L), which can be calculated from its density (1 g/mL) and its molecular weight (18 g/mol)?

Whether a reaction proceeds or not, and to what extent, is a key experimental fact. Hundreds of observations about chemical reactivity have allowed people to come up with generalizations about the chemistry of different combinations of atoms. Quantitative measurements allow comparisons, rankings, and trends to be assigned.

Functional Groups. As the field of organic chemistry was developing, chemists noticed that recurring patterns of atoms also gave comparable results in their chemical reactions. These recurring patterns of atoms, in molecules, are called functional groups (i.e., the groups of atoms that gave rise to the properties, or functionality, of a molecule).

Groups are identifiable portions of a molecule that, in combination, give the molecule itself. The oxygen-hydrogen ("-OH") atom pair in ethanol (CH_3CH_2OH) is called a hydroxyl functional group; the "CH_3CH_2-" portion of the molecule is also a group, and it is thought of as being related to its closest hydrocarbon, where it is attached to a hydrogen atom (CH_3CH_2-H, or CH_3CH_3, called ethane). The "CH_3CH_2-" group is called an ethyl group. Saturated hydrocarbon groups such as ethyl are generically referred to as alkyl groups, and they are generically symbolized by the letter "R-", derived from the historical term for a group, which was "radical" (we now use the word radical differently, to represent an unpaired electron atom). The ethanol molecule, then, is made up of an ethyl group (CH_3CH_2-) attached to a hydroxyl functional group (-OH). Ethanol is given the molecular classification of being an "alcohol"

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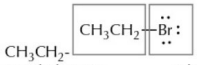
or more explicitly, an example of an "alkyl alcohol." The most generic abbreviation for the family of compounds called alkyl alcohols would be ROH. Figure 0204 contains a few examples of functional groups and names, so that you can see how they are used. We are not taking up the formal system of naming at this point, but if you are interested in this topic, there are Appendices with the rules of naming and many examples of functional groups.

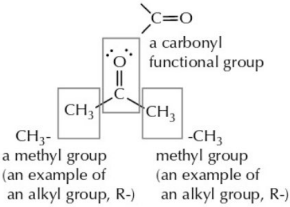
Figure 0204
Examples of functional groups and generic symbolic representations of molecules.

ethanol is an example of an alkyl alcohol (ROH)

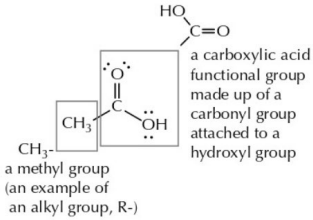
bromoethane is an example of an alkyl bromide (RBr) or more generically an alkyl halide (RX)



acetone is an example of a ketone ($R_2C{=}O$)

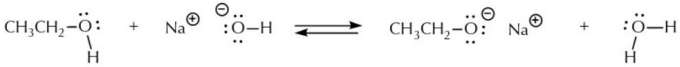


acetic acid is an example of a carboxylic acid (RCO_2H)



Reactivity. Each functional group has its characteristic reactions. For example, the hydroxyl groups of alcohols can react with bases, such as sodium hydroxide, in the reaction shown in Figure 0205.

Figure 0205
The reaction of ethanol with sodium hydroxide.



ethanol, in which "OH" is a hydroxyl functional group, and a source of hydroxide ion

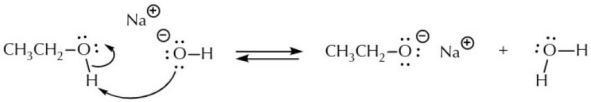
sodium hydroxide, in which "OH" is the hydroxide ion

sodium ethoxide, which is generically symbolized as RO- and is analogous to hydroxide ion (HO-)

water, in which "OH" is not an ion and which is analogous to ethanol and other ROH in general

If it is known that the reaction occurs in a 1-step mechanism, the curved arrow notation can be used to further illustrate the reaction (Figure 0206).

Figure 0206
The curved arrow mechanism for the reaction of ethanol with sodium hydroxide.



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Ethanol loses a proton in this reaction to give an oxygen anion, while hydroxide gains that proton to form a water molecule. Sodium ion is a spectator ion and not involved with the bonding change. Possible ways to express this are that:

- the ethanol molecule was deprotonated by the hydroxide ion
- the hydroxide ion was protonated by the ethanol molecule
- the overall transformation is a proton transfer reaction, as a proton is transferred from one of the oxygen atoms to the other

The measured equilibrium constant for this reaction is about 1, which is perhaps not surprising when you compare the left- and right-hand sides of the chemical equation. There is an oxygen anion on the left (attached to a hydrogen atom) and an oxygen anion on the right (attached to an ethyl group); and there is OH bond on the left (that breaks) and an OH bond on the right (that forms). The observed equilibrium constant of about 1 implies that the relative stabilities of the two oxygen anions is about the same, and the two OH bond strengths are about the same.

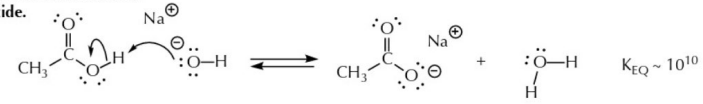
In Figure 0207, another molecule with an OH bond is illustrated: acetic acid. There are a few questions that you might ask:

(a) Does the OH bond in acetic acid react with sodium hydroxide comparably to the OH bond of ethanol?
(b) How does the extent of the reaction of acetic acid with sodium hydroxide (K_{EQ}) compare with that of the reaction with ethanol?

Without a theory, these are questions that need to be answered with experimental results, which are shown in Figure 0207.

Figure 0207

The products, mechanism, and K_{EQ} for the reaction of acetic acid with sodium hydroxide.



The two reactions are analogous. The 2-arrow mechanism is the same for both examples. However, the experimentally determined extent of the reaction lies significantly more to the right than the reaction with ethanol. At first glance, the oxygen anions and OH bonds look as similar in this reaction as in the reaction with ethanol. But the experimentally determined equilibrium constant indicates that there is a significant difference in these reactions (under the same conditions, K_{EQ} is about 1 for ethanol plus NaOH, and about 10^{10} for acetic acid plus NaOH).

B. Using Delocalized Electrons to Explain Structure and Reactivity

The previous section ended with an unanswered question: Why are the equilibrium constants for the reactions of ethanol and acetic acid with sodium hydroxide so different?

To answer this question, chemists would look to any relative differences between the reactants and the products (Figure 0208). The first comparisons would be for relative stability: (a) is there any obvious difference in strength between the OH bond in acetic acid and the OH bond in ethanol that would suggest that the OH bond in acetic acid breaks more easily (sending the reaction to the right); or (b) is there any obvious difference in the oxygen anion that forms from ethanol relative to the one formed from acetic acid that would suggest that the oxygen anion derived from acetic acid is more stable (pulling the reaction to the right); or both?

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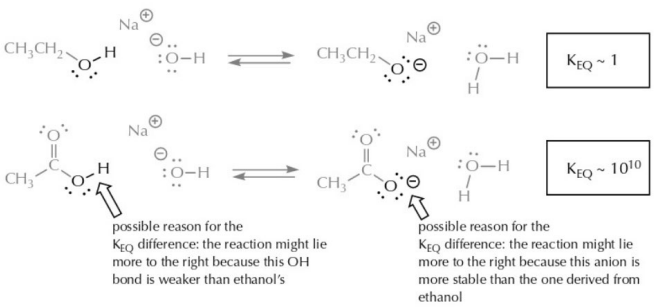

Figure 0208
Exploring possible explanations for the difference in reactivity between acetic acid and ethanol.

The standard criteria for assessing molecular stability do not seem to help resolve this question:

(a) All of the atoms are closed shell.
(b) The number and type of charges are the same.
(c) Both of the anions are located on oxygen atoms.
(d) There is no difference in proximity that the negative charge has to the positive charge of the oxygen atom nucleus.

The actual explanation is a critically important aspect of understanding organic molecular structure: Some electrons are localized (centered as nbe on atoms or as shared 2-electron bonds) and some electrons are delocalized (spread out over more atoms than is obvious from the structural drawing).

Put most simply, our drawing system creates an expectation in our minds that the molecular world is digital, that is, that bonds only occur in integral units (single, double, triple), as do charges (-1, 0, +1). Instead, the molecular world is perfectly analog, and both bond distances and charges can occur over a full range of values.

When you look at the drawing of the anion derived from acetic acid, you might reasonably predict that the two carbon-oxygen bond distances would be quite different, as one is a double bond (shorter) and the other is a single bond (longer). And if you could determine it, you would anticipate that the oxygen atoms are also different, as one is uncharged and the other is an anion. Experimentally, however, the situation for this anion is quite different from these expectations. The two CO bond lengths are exactly equal, with distances that are intermediate between a single and a double bond; and the two oxygen atoms split the negative charge evenly. The actual structure is quite different than what is implied by the normal drawing (Figure 0209).

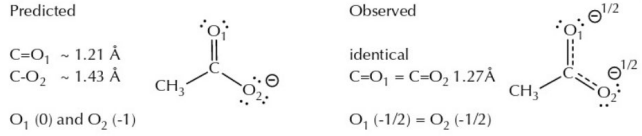

Figure 0209
Difference in predicted and experimental structural data for the anion derived from acetic acid.

The interpretation of the experimental structure is that two of the electron pairs (an nbe pair from one oxygen and one of the bonds from the double bond) are spread out (delocalized) over the three-atom O-C-O system. In a real sense, the fourth criterion (d, above) for stability is being invoked: The negative

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charge does have greater proximity to positive charge because it is being associated with more than one nucleus. Instead of only being located on one of the oxygen atoms, the experimental result suggests that the electron pair is distributed over three nuclei, which provides more significant electrostatic stabilization for the negative charge compared with its being concentrated on one atom. All of the other electrons are considered to be localized (fixed in place), and the atoms themselves remain in their same relative positions (connectivity is maintained).

As you might have already concluded from the drawing in Figure 0209, electron delocalization presents a significant challenge for drawing accurate molecular structures. The anion derived from acetic acid is only one structure, with one set of bond lengths and one value for the charge on each atom. Unfortunately, our standard Lewis structures are really not up to the task of drawing actual molecular structures when partial bonds and charges are present. The next section introduces how chemists have elected to solve the representational challenge created by a world filled with molecules that have a wide and continuous spectrum of bonding and electronic charges.

C. Using Resonance Contributors to Represent a Molecular Structure with Delocalized Electrons

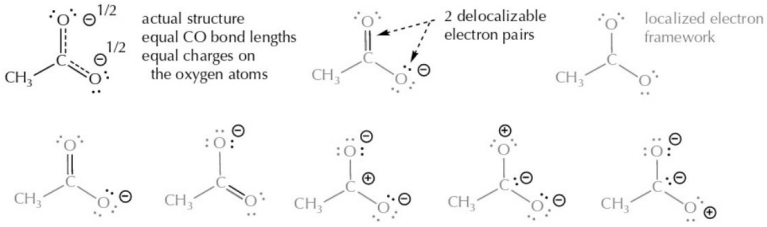
Chemists had the option to develop a new drawing system that would code for partial bonds and fractional charges. Fortunately, we did not do this. A drawing system that needs to represent the difference between 1.2, 1.4, 1.5, and 1.7 bonds, for instance, would be complicated, to say the least. Imagine the challenge of remembering and interpreting such a system! And more importantly: how to know, other than with endless lists of experimental values, what the values are for the different bond lengths and partial charges? Such a drawing system would be difficult, if not impossible, to learn, use, and keep track of.

Instead of creating an unwieldy system for representing partial bonds and charges, chemists recognized that most electrons are localized, and there is no variation needed for the way they are drawn. The delocalizable electrons could be distributed differently, on this localized electron framework, and create different drawings for the same molecule based on the placement of the delocalizable electrons.

Using the anion derived from acetic acid, once again, there are two electron pairs that, when we imagine them as delocalized, account for the experimental observations about the bond lengths and charges. The remaining electron pairs are the localized ones, using a negative definition: Localized electron pairs are the ones that are not delocalized. In Figure 0210, the imagined delocalized electron structure of the actual molecule is re-imagined as a set of drawings where the two delocalizable electron pairs are redistributed in ways that maintain the localized electron framework.

Figure 0210

Actual structure for the anion derived from acetic acid.



five drawings with the delocalizable electrons redistributed on the localized electron framework; all localized electrons and atoms are fixed in space and only the delocalizable electrons are changed

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The collection of drawings in Figure 0210 is how chemists account for delocalizable electrons in molecular structures. We acknowledge that none of the structures is accurate, but that, collectively, the actual structure has aspects of these individual drawings, which we call the resonance contributors to the actual (single) structure. The resonance contributors to the actual structure are linked together by the double-headed arrow (Figure 0211). Symbolically, the double-headed arrows are reserved exclusively to indicate a collection of resonance contributors.

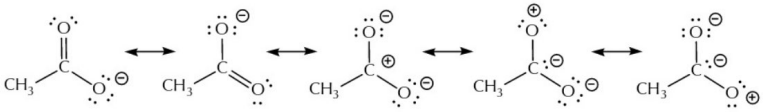
Two important ideas about resonance contributors that beginning learners often fail to appreciate are worth emphasizing here.

First, although the delocalizable electrons in these drawings are being redistributed as you move from one contributor to the next, always remember there is only one actual structure, made up of partial bonds and partial charges, and that you should draw no inference whatsoever that the electrons are moving around or bouncing back and forth between the atoms. You might also find people, including internet sources, who use the verb form resonate ("the electrons resonate"), when talking about delocalization, which also implies a model of electron movement. This verb is as inaccurate as it is annoying. Delocalization is not a phenomenon that starts and stops and involves a process comparable to a chemical reaction. The term "resonance" applies to a particular case of delocalization (there are others), and resonance contributors are used, as described here, to compensate for our decision to not create a drawing system that quantitatively accounts for partial bonds and charges.

Second, the redistribution of electrons in these drawings is taking place along the localized electron framework. Because there is only one actual structure, the localized electrons and the atoms are fixed in space and cannot be relocated from drawing to drawing, and must be, by definition, identical as you move from one resonance contributor to the other. The localized electron structure, and all of the atoms, provides the fixed drawing platform on which the delocalizable electrons are shown.

Figure 0211

Rather than drawing the actual structure for the delocalized anion derived from acetic acid, a collection of resonance contributors is used.



five resonance contributors used to represent the single molecular structure of the anion derived from deprotonating acetic acid

The key idea to understanding resonance contributors is stated in both of those important ideas, above: There is only one actual structure, and we do not have a system that we can use to represent that single structure with a single drawing. Rather, we use a set of drawings where atoms and localized electrons are fixed in space as the conserved pieces, and then show the possible redistribution of the delocalizable electrons, resulting in a set of fictitious Lewis structures. Individually, none of these drawings is an accurate representation of the real, delocalized structure. Instead, the relative contributions of these individual drawings to what we imagine the real structure to be can be assessed. The individual resonance contributors can be ranked according to the usual rules for stability (closed shell atoms, uncharged atoms, placement and proximity of charges). In this set of drawings (Figure 0211), the first two drawings are equivalent to each other, but not identical drawings because the atoms and localized electrons are fixed in space. These two drawings represent contributors to the actual structure that are both more significant than any of the other three because they both possess all closed shell atoms and the others do not.

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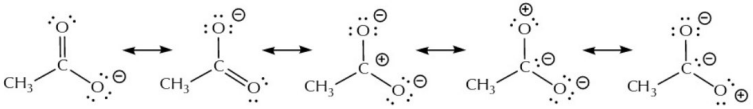
In general, resonance contributors with all closed shell atoms and no formal charges outside of the [-1, 0, +1] range are the most significant to describing the actual structure. For the anion derived from acetic acid, only two of the five resonance contributors meet both of these criteria (Figure 0212). These two are the major, or significant, contributors to the actual structure. By inspection, these two drawings are equivalent contributors because they have the same set of bonds and charge placement, and the actual structure is imagined to be midway between these two resonance contributors (return to Figure 0209 for an interpretative drawing of the actual structure, with its partial bonds and partial charges).

Figure 0212

Value of the five resonance contributors.



two most signficant resonance contributors, which have all closed shell atoms and charges within the [-1, 0, +1] range; these two are equivalent contributors to the structure

these three are less significant contributors to the structure because they have open shell atoms and a greater number of formal charges; of these three minor contributors, the first one is more significant than the other two because the open shell cation is on the less electronegative carbon atom and the anions are on the more electronegative oxygen atoms

Evaluation of the significance of the five resonance contributors is based on the usual guidelines for evaluating molecular structures.

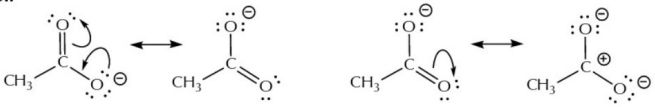
Another reminder, for good measure:

> *A molecule is not zipping back and forth between its resonance contributors; the molecule has the good sense to be in just one actual form, in this case made up of two CO bonds of equal length that sit somewhere in between a standard CO single bond and a standard CO double bond. We humans are the ones who have resorted to using a collection of inaccurate drawings to represent the molecule, and then leave it up to our imaginations to think about what the real structure must be.*

The curved arrow notation can be used to link the different resonance contributors to each other (Figure 0213). Using this notation for linking resonance contributors does not mean that a chemical reaction is taking place, or that this is a phenomenon involving electron movement, as it does in representing mechanisms. Nothing is "resonating." The curved arrow notation, used when drawing resonance contributors, is merely a convenient bookkeeping method for keeping track of the delocalizable electrons as you draw the resonance contributors.

Figure 0213

Using the curved arrow notation to link the relationship between resonance contributors.



The system for localized electron drawing that you have been using all along is used to represent organic molecules, so you don't have to try to draw the delocalized electron structures. This decision creates a

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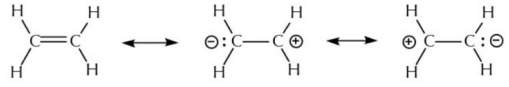
challenge both for drawing structures—because you are not representing everything you know about the molecule—and for reading structures—because you need to learn to take an inventory of the localized and delocalized electrons in every structural drawing, as a part of your understanding of an organic molecule, much the same way you need to inventory whether the atoms are closed shell or have the appropriate formal charge.

D. Predicting Delocalizable Electrons, Drawing Resonance Contributors, and Evaluating Resonance Contributors

The assignment of which electrons are delocalized and which ones are localized is not coded explicitly into drawings, but rather is left for the reader of a drawing to determine. Fortunately, the guidelines for identifying delocalizable electrons are quite systematic and unambiguous and have only a few special circumstances where there are exceptions to remember.

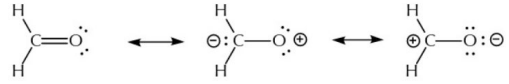
All multiple bonds have delocalizable electrons. Double bonds have one delocalizable electron pair, and triple bonds have two, regardless of the involved atoms. These delocalizable pairs can be redistributed on the localized electron framework, maintaining the connectivity and position of the atoms. Double bonds can be represented by a set of three resonance contributors, and triple bonds can be represented by a set of four contributors (Figure 0214). In these examples, as is nearly universally true, we draw the most significant contributor when we write out the compound, particularly when all of the atoms have closed shell configurations and they are uncharged. Other resonance contributors would be ranked as minor, and evaluated according to having open shell atoms, formal charges, and the placement of the formal charges. As illustrated in Figure 0214, these molecules have a single major resonance contributor (all atoms closed shell and uncharged), and those three drawings would be used by anyone representing those compounds. All of the other resonance contributors are less significant because they have open shell atoms.

Figure 0214
Resonance contributors for double and triple bonds.



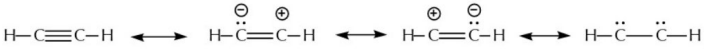
major contributor: all closed shell atoms

two minor contributors: open shell atoms both are equivalent contributors



major contributor: all closed shell atoms

two minor contributors: open shell atoms the one on the right is more significant than the one on the left: charge placement



major contributor: all closed shell atoms

three minor contributors; the two on the left are equivalent and they are more significant than the one on the right, which has two open shell atoms

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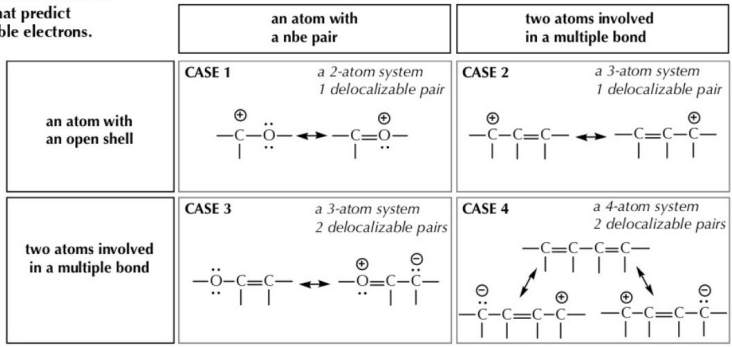
Combinations of multiple bonds, open-shell atoms, and atoms with nbe. There are four fundamental combinations of structural sub-units that cover the range of options for predicting which electrons in an organic molecule are predicted to be delocalizable. The 2 x 2 grid, along with representative examples, is shown in Figure 0215, with each of the four cases discussed in detail, below.

Figure 0215

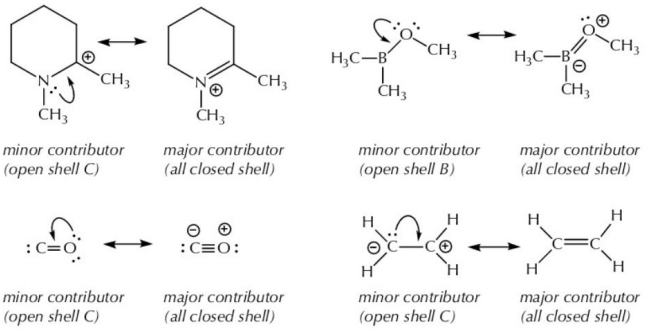
Four fundamental cases for combinations of structural subunits that predict delocalizable electrons.



CASE 1: An open shell atom attached to an atom with a nbe pair (a 2-atom system). As described in Section 1.4B, achieving a closed shell configuration drives the chemistry of open shell atoms. When an open shell atom is directly attached to another atom that possesses a nonbonding electron pair, the electrons can be shared and result in both atoms having closed shells. In Figure 0215, an open shell (sextet) carbocation is attached to an oxygen atom (CASE 1), and the delocalized form, in which one of its electron pairs is shared, is the significant resonance contributor because all of the atoms are closed shell. This contributor, containing the double bond, is so significant that, experimentally, the CO bond length in such a molecule is quite close to a standard CO double bond. The experimental bond length, which points to the significance of the atoms having closed shell configurations, is consistent with the fundamental ideas about organic molecular structure that have been presented so far in this book. The contribution of all closed

Figure 0216

Delocalization involving CASE 1.


minor contributor (open shell C)
major contributor (all closed shell)
minor contributor (open shell B)
major contributor (all closed shell)
minor contributor (open shell C)
major contributor (all closed shell)
minor contributor (open shell C)
major contributor (all closed shell)

Delocalization involving CASE 1, an open shell atom attached to an atom with a nbe pair (a 2-atom system).

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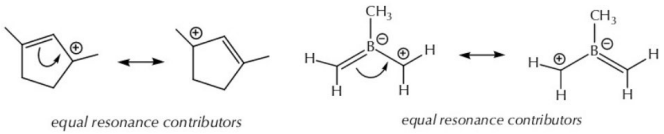
shell atoms is much more important to a structure than placing the positive charge on the less electronegative carbon atom, which requires the open shell contributor. Some representative examples of CASE 1 are shown in Figure 0216. Note that CASE 1 is actually the same as the "all multiple bonds are delocalizable" category, from earlier in this section: an open shell carbon attached to a carbon with a nbe pair is the minor resonance contributor to the structure of a carbon-carbon double bond. In every example in Figure 0216, the all closed shell atom resonance contributor is by far the most significant.

CASE 2: An open shell atom attached to an atom involved in a multiple bond (a 3-atom system). Another source of delocalizable electrons for an open shell atom is a multiple bond. When the open shell atom is part of a 3-atom system where it is attached to an atom that is involved in a multiple bond, a 2-electron bond can be delocalized over the atoms. Unlike the first case, however, completing the octet for the original open shell atom results in another open shell atom at the other end of the 3-atom chain. The question of which is the more significant contributor is a complex topic that will be taken up later, and so a couple of symmetrical examples are shown in Figure 0217, representing cases where the two contributors are equivalent.

Figure 0217
Delocalization involving CASE 2.

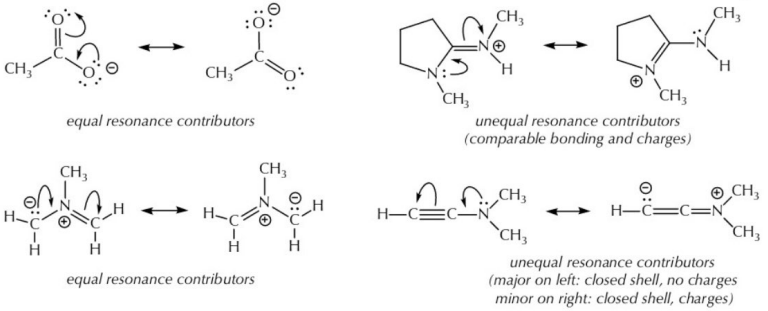


Delocalization involving CASE 2, an open shell atom attached to an atom involved in a multiple bond (a 3-atom system).

CASE 3: An atom with a nbe pair is attached to an atom involved in a multiple bond (a 3-atom system). This 3-atom system is by far the most common one that you will encounter, because both of the resonance contributors have all closed shell atoms, and this is the only case in which that is always true. This case includes the anion derived from acetic acid, which was used to introduce delocalization in the previous section.

Examples of CASE 3 are shown in the Figure 0218. Three of the four examples are symmetrical, and the two drawings are expected to equal contributors to the actual structure. In the first example, although the atoms in both resonance contributors are all closed shell atoms, the contributor drawn on the left comprises uncharged atoms, while the one on the right, with formally charged atoms, would be a less significant contributor to the structure.

Figure 0218
Delocalization involving CASE 3.


equal resonance contributors
unequal resonance contributors
(comparable bonding and charges)
equal resonance contributors
unequal resonance contributors
(major on left: closed shell, no charges
minor on right: closed shell, charges)

Delocalization involving CASE 3, an atom with a nbe pair attached to an atom involved in a multiple bond (a 3-atom system).

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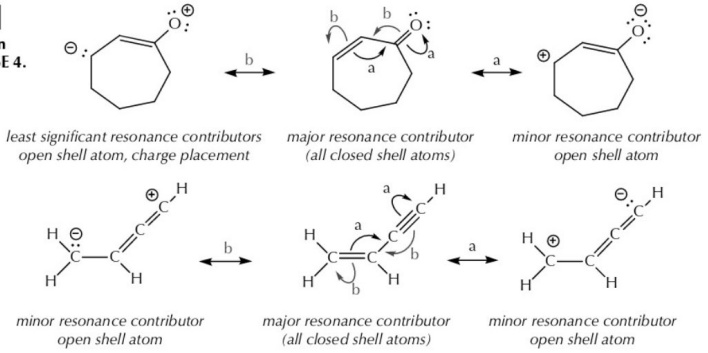
CASE 4: A multiple bond attached to an atom involved in another multiple bond (a 4-atom system). Multiple bonds attached together, but not sharing an atom, create a 4-atom chain over which delocalization can occur. In showing the electron redistributions in the resonance contributors, one of the multiple bonds is the electron source and the other is the destination. As with the individual multiple bonds, open shell atoms and charges result, so these resonance contributors are minor compared with the all closed shell atom form, particularly when the atoms are also uncharged. Two examples from CASE 4 are shown in Figure 0219. The drawings on the left, in both cases, are by far the more significant contributors to the actual structures, and the molecules themselves would always be represented using these drawings.

The lesson here and throughout these cases, however, is that these drawings are not the full picture of the actual structure, and you must begin to consciously and then subconsciously take an inventory, in every organic structure you see, to assess whether there are delocalizable electrons and what effect delocalization might have on the structure and/or reactivity of these compounds. Rest assured, this theme will recur frequently and with many reminders.

Figure 0219
Delocalization involving CASE 4.



Delocalization involving CASE 4, two multiple bonds (a 4-atom system).

The four cases are a basis set of situations where delocalization can be anticipated, an alphabet from which more complex examples are constructed. Many molecules possess combinations of these cases, and while the delocalizable electrons can be readily identified, constructing a full set of resonance contributors can become more challenging because the number of possible contributors can increase substantially.

Fortunately, the least significant resonance contributors are usually ignored because the properties of the compound are highly correlated with the more significant contributors. As a consequence, you will rarely need to think about all of the resonance contributors, but you will rather focus on the more significant ones (closed shell atoms, limited formal charges). Accordingly, drawing a full set of resonance contributors is less daunting if you are restricted, for instance, to only showing contributors with all closed shell atoms and formal charges in the [-1, 0, +1] range. In Figure 0220, the total number of delocalizable electron pairs for some molecules with combinations of these four cases is shown, along with the construction of one other resonance contributor that maintains all closed shell atoms and formal charges in the [-1, 0, +1] range.

The compound in the fourth example in Figure 0220 is named benzene. Benzene represents a case where the alternating doubles bonds around the ring means that it is possible to construct an equivalent resonance contributor with all closed shell atoms that are also uncharged. This is a relatively rare feature for a delocalized electron structure. Structurally, all of the CC bond distances in benzene are equal (at about 1.5 stan-

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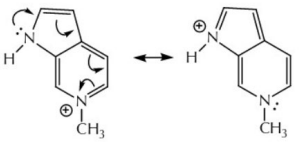
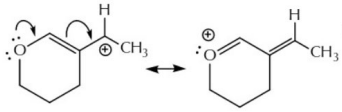
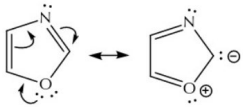


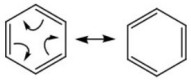
4 delocalizable electron pairs over 7 atoms



2 delocalizable electron pairs over 4 atoms



3 delocalizable electron pairs over 5 atoms



3 delocalizable electron pairs over 6 atoms

Figure 0220
Delocalization involving combinations of the four fundamental cases.

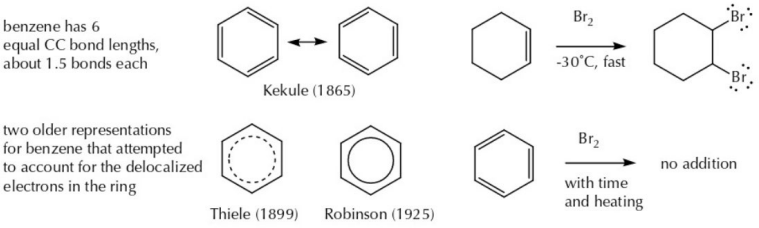
dard CC single bonds), and this delocalization provides benzene with far less reactivity than other comparable molecules. With one or two double bonds in the ring, for example, addition reactions occur quite readily.

On the other hand, benzene does not participate in these addition reactions at all (Figure 0221). A few different representations have been used for benzene over the years, and you might encounter these drawings in other settings. We will stick with one of the two resonance contributors that displays the three double bonds—but automatically understand that there is a second, equally significant resonance contributor to its structure that profoundly influences its chemical properties. As you might encounter from other resources, the delocalization stabilization present in benzene is exceptionally high, and is historically known by the term "aromaticity."

The details and ramifications of this stabilization on both the structure and reactivity of benzene, and an entire class of molecules classified as aromatic, is presented in Book B, Chapter 10. For now, you may simply remember that the benzene ring is particularly stable thanks to its special form of delocalization, and that it does not exhibit the same reactivity as other compounds containing double bonds. Historically, this difference in reactivity gave rise to chemists using special representations to symbolize the bonds in benzene. Johannes Thiele, in 1899, proposed a representation of benzene with a dotted-line circle to denote partial valence (electrons were not yet discovered or used as the basis of the chemical bond). Robert Robinson, in 1925, proposed the solid-line circle, and this was used ubiquitously for about 60 years. Drawing curved arrow mechanisms using that circle is impossible, and the chemistry community has shifted back to using one of the two equivalent resonance contributors since the 1990s.

Figure 0221
Delocalization in benzene.

The delocalization in benzene results in double bonds that are not as reactive as others.


benzene has 6 equal CC bond lengths, about 1.5 bonds each
Kekule (1865)
Br2
-30°C, fast
two older representations for benzene that attempted to account for the delocalized electrons in the ring
Thiele (1899)
Robinson (1925)
Br2
with time and heating
no addition

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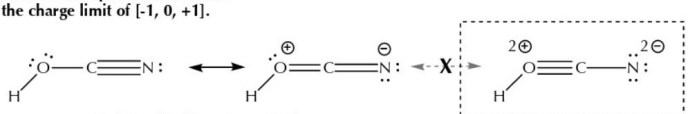
There are three cautions about identifying delocalizable electrons to keep in mind.

CAUTION 1. Resonance contributors with atoms with formal charges outside of the [-1, 0, +1] range are insignificant. As a general rule, you have already learned that main group organic elements do not easily achieve formal charges outside of the [-1, 0, +1] range, and so proposing either a +2 or -2 charge is also an exceptional case and would require experimental evidence to support it. If what looks to be an otherwise delocalizable electron pair would create a resonance contributor with a formal charge outside of the [-1, 0, +1] range, then the default choice (absent evidence) is that the electron pair is localized and not delocalized. A nice example of this is provided by cyanic acid, HOCN (Figure 0222). With two delocalizable pairs included in the triple bond, it is tempting to say that both of the nbe pairs on the oxygen atom are delocalizable, and to conclude that there are 4 delocalizable pairs in HOCN. But when you construct the other possible resonance contributors, you end up with one that has a +2 charge on the oxygen atom and a -2 charge on the nitrogen atom. This potential resonance contributor is ignored because of those +2 and -2 charges, and the second nbe pair on oxygen is considered localized. The experimental structural data for the actual HOCN molecule (bond angles and distances) is consistent with this conclusion, which is where the generalization to exclude such contributors comes from.

Figure 0222

Delocalization is not anticipated when atoms must exceed the charge limit of [-1, 0, +1].



3 delocalizable pairs, not 4, because delocalization of the second nbe pair on oxygen gives +2 and -2 charges in the third resonance contributor

CAUTION 2. Contributors that form linear geometries within rings that are too small are not possible. Although the details of predicting geometry around atoms is taken up in detail in the next section, two observations that include geometry are relevant to this second caution about identifying delocalizable electrons. Because the bond angles inside of a ring of atoms are quite naturally nonlinear (you cannot form a circle from a straight line), groups of atoms with known linear geometries are difficult to impossible to incorporate into ring structures that are too small in size.

We can look at a few experimental facts to illustrate the point. For example, triple bonds are linear over a 4-atom strand, and the smallest hydrocarbon ring with a triple bond in it has 8 carbons (cyclooctyne). Another linear set of atoms can be found when two double bonds are co-joined and share an atom (C=C=C). This is called an allene, or a cumulative double bond structure, and it is linear at the central atom. The 9-membered ring hydrocarbon is the smallest stable ring that is observed to hold an allene (1,2-cyclononadiene) (Figure 0223).

Figure 0223

The smallest stable examples of cyclic hydrocarbons with a triple bond or an allene in the ring.

cyclooctyne 1,2-cyclononadiene

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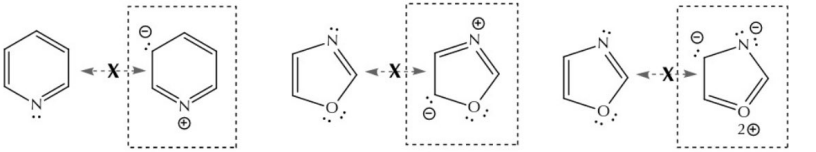
Consequently, if electron delocalization would result in either a triple bond or an allene structure within a small ring (less than 8 or 9 atoms in size), that delocalization is not proposed to take place and the corresponding electron pair is deemed to be localized. Some molecular structures where nonbonding electron pairs are localized due to these criteria are shown in Figure 0224.

Figure 0224

Delocalization is not anticipated when linear atoms (triple bonds, allenes) are formed in small rings.



not a resonance contributor: allene in a small ring

not a resonance contributor: allene in a small ring

not a resonance contributor: allene in a small ring +2 charge on O

CAUTION 3. Keep an eye on the other normal bonding rules for organic main group elements as you explore the possibilities for electron delocalization. As you focus on one thing (delocalization), it can become easier to accidentally ignore the basic ground rules for rational organic structures. Be sure to double check that you are (a) drawing resonance contributors in which all of the atoms are present (conservation of atoms), (b) checking that the overall charge is the same (charge balance), and (c) not exceeding octets or neglecting nonbonding electron pairs (periodic behavior).

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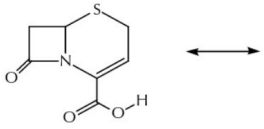
PRACTICE QUESTIONS

2.01 For each of the following pharmaceutically active medications:
(i) provide the missing nonbonding electron pairs
(ii) identify the total number of delocalizable electron pairs
(iii) draw another resonance contributor for the molecule using the curved arrow notation to indicate the redistribution of electrons between the two forms
(iv) evaluate the two contributors and circle the more significant contributor to the actual structure, or if they are equivalent
(v) provide a brief explanation for your selection
If the molecule has no delocalizable electron pairs, indicate the number as "0" and ignore parts (iii) and (iv) for that example. Note that there may be a large number of possible resonance contributors, so this is a great problem for making comparisons with peers and debating the relative merits of your answers.

(a)

cephem

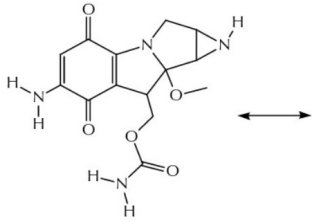


explanation for your selection of the major contributor, or the lack of one:

number of delocalizable electron pairs:

(b)

mitomycin

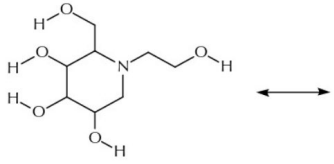


explanation for your selection of the major contributor, or the lack of one:

number of delocalizable electron pairs:

(c)

miglitol



explanation for your selection of the major contributor, or the lack of one:

number of delocalizable electron pairs:

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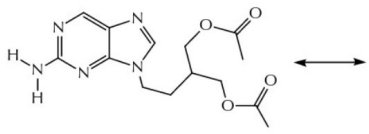
2.01 (cont.)

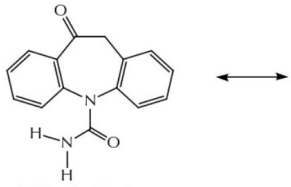
(d) famciclovir



number of delocalizable electron pairs:

explanation for your selection of the major contributor, or the lack of one:

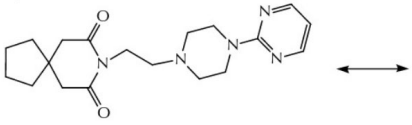
(e) oxacarbazepine



number of delocalizable electron pairs:

explanation for your selection of the major contributor, or the lack of one:

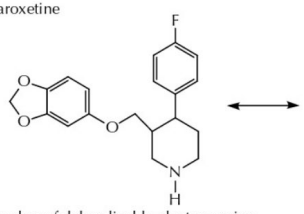
(f) buspirone



number of delocalizable electron pairs:

explanation for your selection of the major contributor, or the lack of one:

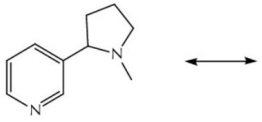
(g) paroxetine



number of delocalizable electron pairs:

explanation for your selection of the major contributor, or the lack of one:

(h) nicotine



number of delocalizable electron pairs:

explanation for your selection of the major contributor, or the lack of one:

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2.02 The bond length that is expected for a boron-chlorine single bond is 1.82 Å. The actual bond length observed for the three B-Cl bonds in boron trichloride (BCl_3) is 1.75 Å. Provide drawings and a brief explanation for this observed difference.

drawings	*explanation*

2.03 The following ions and molecules have at least one resonance contributor with all closed shell atoms. Draw all of the closed shell atom resonance contributors for each of these examples. Names and connectivities are given, followed by the more conventional condensed formula in parentheses when it is different from the connectivity. For atoms bonded to multiple oxygen atoms, assume that the oxygen atoms are each bonded to that atom as the central atom and not to each other. Include formal charges and nonbonding electron pairs.

(a) bicarbonate ion, $HOCO_2^{\ominus}$ ($HCO_3^{\ominus}$)

(b) formaldehyde, H_2CO

(c) nitrite ion, $ONO^{\ominus}$ ($NO_2^{\ominus}$)

(d) isocyanide ion, $NCO^{\ominus}$

(e) ozone, OOO (O_3)

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(a) bicarbonate ion, $HOCO_2^{\ominus}$ ($HCO_3^{\ominus}$)

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(e) ozone, OOO (O_3)

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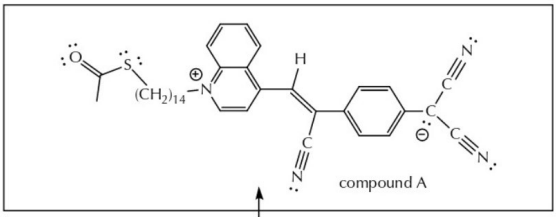
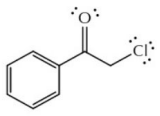
2.04 Researchers are devoting significant effort to discovering organic compounds that can serve as conductors of electricity and/or as components of electric circuits. Compound A, shown below, has properties that may be useful as a rectifier (a device that controls which way electrons flow through it).

Draw a resonance contributor for compound A that has no formal charges on any of the atoms. Use the curved arrow notation, on the structure shown, to indicate the redistribution of the delocalizable electrons.

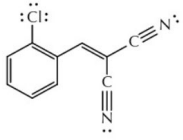


2.05 Draw all of the other closed shell atom resonance contributors for (a) "CN," the active ingredient in the original formulation of Mace (tear gas), and for two other closed shell atom resonance contributors for (b) "CS," the more modern agent that is used. For CS, show a contributor where a negative charge is on a carbon atom and another where the negative charge is on a nitrogen atom.

(a)



(b)



(c) Draw two structural isomers of CN that have a greater number of all closed shell atom resonance contributors than CN does.

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2.2 Bonding Models That Account for Molecular Structure and Properties

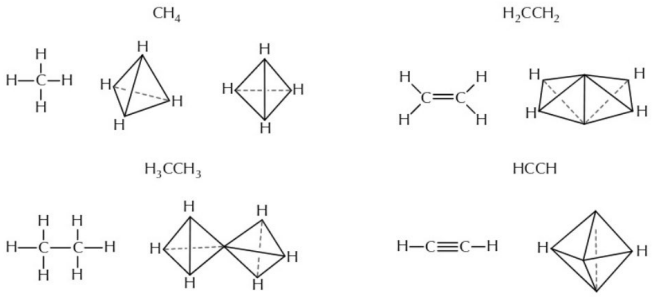
A. Molecular Geometry Centered at Atoms: The VSEPR Model

Experimental information about the three-dimensional geometry of atoms in space was not possible until after the discovery of x-rays (1895) and the development of x-ray crystallography. Sodium chloride (table salt) was the first substance whose three-dimensional crystal structure was determined (1913), and small organic molecules followed a decade later (1923). The first large organic biomolecule (myoglobin, a protein) whose three-dimensional structure was determined did not take place until 1958.

Recall that humans created the idea of molecular connectivity to solve a problem in understanding isomerism (Section 1.1C). In the mid-1860s, about 50 years after creating the idea of molecular connectivity, humans invented an idea about the arrangement of atoms in space to solve another isomerism puzzle they were trying to explain. This general topic, called stereoisomerism (isomers that result from three-dimensional arrangements) is the topic of Chapter 5. For now, we will simply report the conclusion from the 1870s: To solve the isomerism problem, people concluded that atoms must be tetrahedral in shape. Drawings such as the ones shown in Figure 0225 were used to represent the three-dimensional shape of molecules. Single bonding was imagined as two tetrahedra sharing a vertex; double bonds shared a side; and triple bonds shared a face. Tetrahedral atoms solved all of the isomerism problems that people were trying to understand, and so the model was widely adopted.

Figure 0225

Historical drawings of tetrahedral atoms and how different bonding was represented.

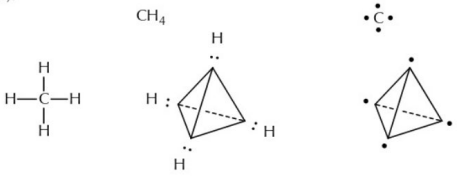


Electrons were discovered in 1897, and it took about 30 years, along with the discovery of the other subatomic particles, for scientists to develop and accept the standard model for atomic structure (in 1920, protons were discovered, and neutrons were postulated, although neutrons were not experimentally identified until 1932).

In 1916, G.N. Lewis, who certainly grew up believing that atoms were tetrahedral, argued for a picture of bonding as shared electron pairs at the corners of those tetrahedral atoms (the first "Lewis dot" drawings for molecular structure) as well as solitary tetrahedral carbon atoms with their four available unpaired electrons ready for bonding (Figure 0226).

Figure 0226

G.N. Lewis, in 1916, drew tetrahedral atoms with shared electron pair bonds.



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Starting in the 1930s, with the 2-electron chemical bond firmly established and accepted as an idea, people began to evolve different ways for representing three-dimensional geometry. Ball-and-stick drawings that suggested perspective through different line weights were used in the 1940s and using heavy and dashed lines to connote the same sense of spatial perspective became common in the 1950s (Figure 0227). By the late 1950s, the "line, dash, and wedge" notation for representing the three-dimensional bonding of groups around a central atom was widely adopted and is now commonplace (Figure 0228).

Figure 0227

Comparison of different representations for combinations of tetrahedral atoms.

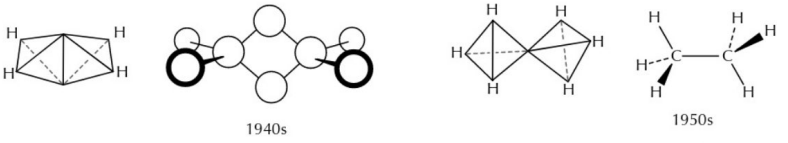
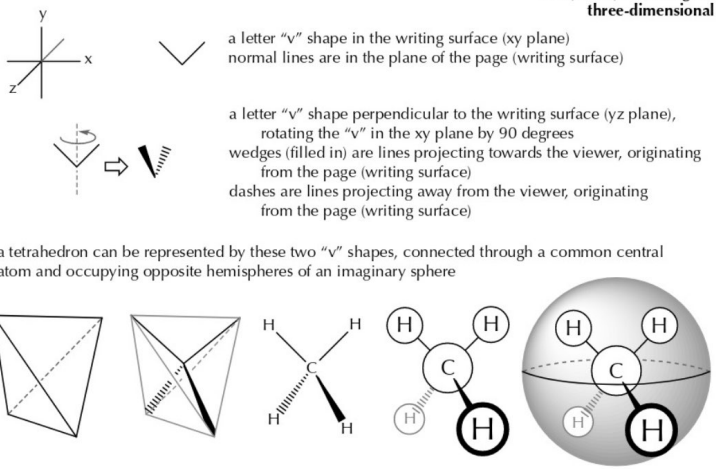


Figure 0228

Line, dash, and wedge notation for three-dimensional drawings.


y
x
z
a letter "v" shape in the writing surface (xy plane)
normal lines are in the plane of the page (writing surface)
a letter "v" shape perpendicular to the writing surface (yz plane), rotating the "v" in the xy plane by 90 degrees
wedges (filled in) are lines projecting towards the viewer, originating from the page (writing surface)
dashes are lines projecting away from the viewer, originating from the page (writing surface)
a tetrahedron can be represented by these two "v" shapes, connected through a common central atom and occupying opposite hemispheres of an imaginary sphere

The idea that the repulsion of valence electrons from one another could be the origin of the geometry of groups bonded to a central atom is reasonable, and models for atomic geometry using this idea date from 1939–40. In 1957, the Valence Shell Electron Pair Repulsion (VSEPR) model was formally presented in the field of chemistry. VSEPR is a localized electron model and provides a way to think about the three-dimensional geometry of the localized electron pairs on organic main group elements. The fact that the organic main group elements are dominated by second row, octet closed shell atoms, means that all of the atoms using organic main group elements have only 4, 3, or 2 localized electron pairs. These numbers correspond to the VSEPR electron domains for dictating the placement of the electrons (electronic geometry) and the shape of molecule as determined by the placement of atoms (observed geometry, which is

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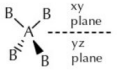
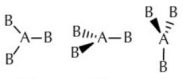
restricted to the placement of atoms because electrons cannot be observed experimentally). The range of geometric outcomes is presented in Figure 0229 and they are exemplified below.

Figure 0229

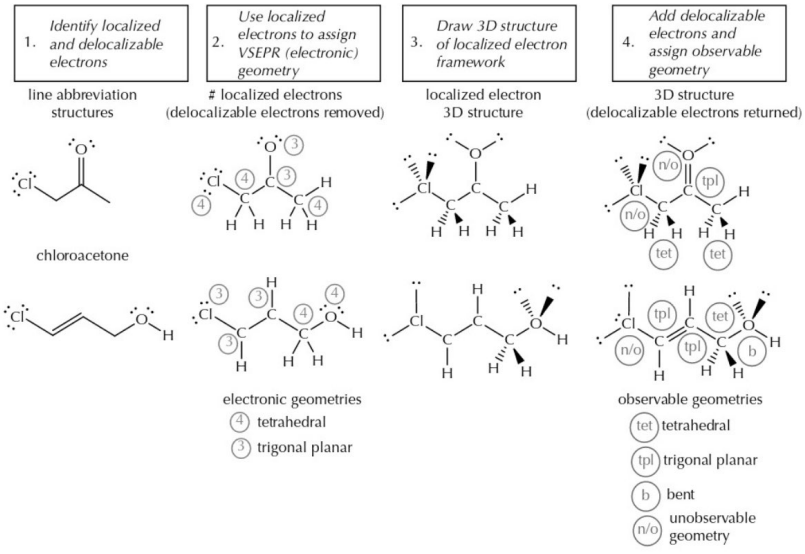
Table of VSEPR electronic and observable geometries for organic main group elements.

# of VSEPR domains (localized electron pairs)	electronic geometry	3D representation	# of localized nbe pairs (observable geometry) 0	1	2	3
4	tetrahedral		(tetrahedral)	(trigonal pyramidal)	(bent)	(unobservable geometry)
3	trigonal planar	 xy plane xz plane yz plane	(trigonal planar)	(bent)	(unobservable geometry)	
2	linear	x axis	(linear)	(unobservable geometry)		

Using two of the three C_3H_5ClO structural isomers from Section 1.2B as examples, the 3D structures and the electronic and observable geometries can be identified for all of the atoms (Figure 0230).

Figure 0230

Progress of line abbreviation to 3D structural drawings.


1. Identify localized and delocalizable electrons
2. Use localized electrons to assign VSEPR (electronic) geometry
3. Draw 3D structure of localized electron framework
4. Add delocalizable electrons and assign observable geometry
line abbreviation structures
localized electrons (delocalizable electrons removed)
localized electron 3D structure
3D structure (delocalizable electrons returned)
chloroacetone
electronic geometries
4 tetrahedral
3 trigonal planar
observable geometries
tet tetrahedral
tpl trigonal planar
b bent
n/o unobservable geometry

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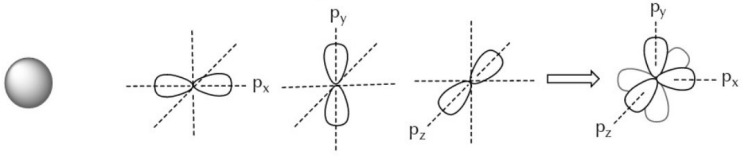
B. The Quantum Mechanics Conundrum

The discovery of the subatomic particles in the early 20th century created an incredible understanding of atomic structure and the layout of the periodic table of the elements. Fundamental elemental identity (placement on the periodic table) was due to the number of protons. The periodic nature of elemental properties was tied to the repeating and growing pattern of sublevels within the major electron energy levels (1s; 2s, 2p; 3s, 3p, 3d; etc.) and how these energy levels filled from lowest energy (closest to the nucleus) to higher energies (the aufbau principle).

A fixed number of orbitals comprises each sublevel (s:1; p:3; d:5), and a finite number of electrons can occupy them (0, 1, or 2 electrons per orbital). Every sublevel is a sphere, in total, but they are all subdivided except for the s levels (that is, taken collectively, the sum of the equations for the 3 p orbitals in a p subshell equals a sphere). We most commonly picture the s and p orbitals according to a set of familiar shapes (Figure 0231).

Figure 0231

Orbitals comprising the s and p sublevels.



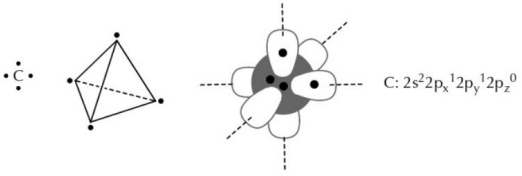
Every element can be described with its electron configuration, and it matches up with how we place elements on the periodic table. Hydrogen is $1s^1$. Beryllium is $1s^22s^2$.

Carbon is $1s^22s^22p_x^{\ 1}2p_y^{\ 1}2p_z^{\ 0}$... and that created a conundrum to solve, historically.

Since the mid-1860s, people believed that carbon was a tetrahedral atom with 4 equivalent valence positions. When electrons were discovered, chemists such as Lewis preserved 60 to 70 years of thinking and simply added electrons onto the preexisting model and naturally concluded that carbon had 4 equivalent electrons with which to make bonds. But in $1s^22s^22p_x^{\ 1}2p_y^{\ 1}2p_z^{\ 0}$ there is one pair of electrons ($2s^2$) and two unpaired electrons that are different from those ($2p_x^{\ 1}2p_y^{\ 1}$). Those 4 electrons are clearly not the same as Lewis's tetrahedron with a dot at each vertex (Figure 0232).

Figure 0232

Two conflicting views of carbon (1920s–1930s).



C. Molecular Geometry Centered at Atoms: The Hybridization Model

There was no experimental technique available for locating electrons in space in the 1920s, and there are still none today.

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The solution to this puzzle, proposed by Linus Pauling in 1931, was that carbon atoms, when in molecules, did not have to conform to the constraints of a lone carbon atom as it appeared on the periodic table. He proposed a mathematical solution to the problem. And although his actual mathematics was complex, because of the equations involving atomic orbitals, his conceptual approach was really quite simple and logical. Pauling took what he had, on the one hand: a carbon with 4 nonidentical orbitals of unequal occupancy (1 s orbital with 2 electrons and 3 p orbitals with a total of 2 electrons). On the other hand, he wanted to form 4 equivalent orbitals with 1 electron each that could be pointed to the corners of a tetrahedron. Like Lewis, Pauling had also grown up believing that atoms were tetrahedral.

Pauling's strategy was exactly the same as solving a word problem from an elementary mathematics class.

Here are the conditions. You have a little bit of money: 400 cents. Of these 400 cents, 100 are from a single American dollar and 300 are from 3 euros. You can give gifts of 100 cents to your friends, so you are limited to a maximum of 4 gifts. Because your friends really like the American money, you agree to always give away the entire dollar, regardless of how many ways you divide up the cash. So, with the 100-cent limit, you will have leftover euro money if you make fewer than 4 gifts. What is the dollar-to-euro cent ratio if you make 100-cent gifts to 4 friends? To 3 friends? And to 2 friends?

You can do that math!

For 4 friends: each gift is a mixture (a hybrid gift) where each person gets 1/4 of the dollar (25 cents; 25% of a dollar) and 3/4 of a euro to make up the difference (75 cents; 75% of a euro). All of your money would be distributed and each of your 4 friends end up with 100 cents of currency, where the dollar-to-euro ratio is 1:3 (or the d^1e^3 hybrid gift).

For 3 friends: each gift is 1/3 of the dollar and 2/3 of a euro. You have 1 euro left over, and each of your 3 friends end up with 100 cents of currency, where the dollar-to-euro ratio is 1:2 (the d^1e^2 hybrid gift).

For 2 friends: each gift is 1/2 of the dollar and 1/2 of a euro. You have 2 euros left over, and both of your friends end up with 100 cents of currency, where the dollar-to-euro ratio is 1:1 (the d^1e^3 hybrid gift).

Pauling's task was exactly the same. On atomic carbon, he has a single s orbital (the dollar) and three p orbitals (the euros). For CH_4, carbon has 4 friends, and Pauling wants to divide the 4 orbitals up to make 4 equal orbitals (equal gifts) because he believed atoms were perfectly tetrahedral and that CH_4 has 4 identical C-H bonds.

You can do Pauling's math. To make 4 equal orbitals from what he had, Pauling concluded that each orbital at carbon is a mixture (a hybrid orbital) where each one gets 1/4 of the original s orbital and 3/4 of an original p orbital. All 4 of your new orbitals would be equal, and each one ends up with an s-to-p ratio of 1:3 (or the s^1p^3 hybrid orbital). Pauling's process is called orbital hybridization, mixing together what you have to get what you want.

Hybridization of atomic orbitals is not a physical phenomenon; it is a mathematical model and there is no direct experimental measurement that can be made to help confirm or reject it. Orbital hybridization provides an intellectually satisfying way to reconcile the idea that the carbon atom in methane (CH_4) ought to have 4 equivalent valence electrons in 4 equivalent atomic orbitals so it can make its 4 equivalent C-H bonds, resolving the idea that the carbon of the periodic table does not provide an equivalent set of 4 electrons to work with. Pauling's idea was that a carbon atom in methane is not constrained to being the lone carbon of the periodic table, and he conserved orbitals by accounting for them.

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Pauling believed that all atoms were tetrahedral, so in 1931 he was only worried about making four bonds and explaining that carbon atoms in molecules were sp^3 hybridized. Within a few years, however, a better understanding of electron delocalization evolved the hybridization model and provided a unified view of the relationship between localized and delocalized electrons from a perspective of bonding.

The conclusion is what matters: In resonance contributors, localized electron pairs reside in hybrid orbitals, while delocalized electrons reside in p orbitals.

Two other hybridizations are required for this. In the money analogy above, you had either 4, 3, or 2 friends, and you gave them gifts where the dollar-to-euro ratio was 1:3, 1:2, and 1:1, respectively. The most common organic main group elements have the same properties: They form chemical bonds with 4, 3, or 2 localized electron pairs.

When 4 localized electron pairs are needed, then 4 sp^3 orbitals account for the full original set of orbitals at the atom (1 s and 3 p). When 3 localized electron pairs are needed, then 3 sp^2 orbitals account for three of the original orbitals (1 s and 2 p), with one p orbital left behind (unhybridized). And when only 2 localized electron pairs are needed, then 2 sp orbitals account for two of the original orbitals (1 s and 1 p), with two p orbitals left behind (unhybridized).

Figure 0233 gives an overview of the progression from the atom orbitals on an organic main group element (an s plus 3 p), to the three bonding situations (# of localized pairs = # of hybrid orbitals needed), to the corresponding hybridization (accounting for where the original orbitals end up), and finally to the geometries and drawings used for the bonding. The s orbital is always used because its spherical distribution and greater proximity to the (positively charged) nucleus makes it more stable for (negatively charged) electrons.

Figure 0233

The three orbital hybridization models common to organic main group elements.

Atomic carbon orbitals	# hybrid bonds needed	hybridization # hybrid orbitals (geometry)	in hybrids % s, % p	# unhybridized p orbitals	hybridized atoms 3D bonding representation (line/dash/wedge = hybrids)
s p p p	4	4 sp^3 (tetrahedral)	25% s, 75% p	0 p	
s p p p	3	3 sp^2 (trigonal planar)	33% s, 67% p	1 p	p_y p_z p_x
s p p p	2	1 sp (linear)	50% s, 50% p	2 p	p_y, p_z

D. A Unified Picture for VSEPR, Hybridization, and Delocalized Electron Structures

The parallel between Figures 0229 and 0233 is not a coincidence.

We think of organic molecules as being made up of a combination of localized and delocalized electrons. Using the analytical process for constructing resonance contributors presented earlier in this chapter (Section 2.1D), you know how to identify the delocalizable electrons, which automatically defines the localized ones.

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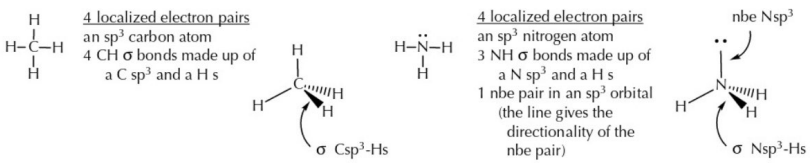
Localized electrons, whether they are covalent bonds or nonbonding electron pairs, reside in hybrid orbitals. The covalent bonds are called sigma (σ) bonds because they possess the components of the s orbital. Localized nonbonding electron pairs are simply given the label of the hybridization (Figure 0234).

Figure 0234

Hybrid orbitals used for localized electron (sigma) bonding and nonbonding electron pairs.


methane CH4
4 localized electron pairs
an sp3 carbon atom
4 CH σ bonds made up of a C sp3 and a H s
σ Csp3-Hs
ammonia NH3
4 localized electron pairs
an sp3 nitrogen atom
3 NH σ bonds made up of a N sp3 and a H s
1 nbe pair in an sp3 orbital (the line gives the directionality of the nbe pair)
nbe Nsp3
σ Nsp3-Hs

Delocalized electrons reside in the unhybridized p orbitals. These p orbitals are not found on sp^3 atoms, but only on sp^2 and sp atoms. This matches your experience in identifying delocalizable electrons. The carbon in methane (CH_4) has 4 localized electron pairs and no delocalizable electrons. This carbon is sp^3 hybridized and has no unhybridized p orbitals.

The relationship implied in that previous paragraph is big news: Delocalized electrons occupy unhybridized p orbitals, while localized electrons occupy the hybridized orbitals. If you can identify the number of localized electron pairs on an atom, then you know its hybridization and you can accurately draw its 3D orbital representation (Figure 0235). This relationship requires only one change in Figure 0233: the first column. The number of localized electron pairs on an atom dictates the number of hybrid orbitals for making sigma (σ) bonds and for holding localized nonbonding electron pairs.

Figure 0235

The number of localized electron pairs corresponds exactly to the hybridization.

# localized electron pairs	# hybrid bonds needed	hybridization # hybrid orbitals (geometry)	in hybrids % s, % p	# unhybridized p orbitals	hybridized atoms 3D bonding representation (line/dash/wedge = hybrids)
4	4	4 sp^3 (tetrahedral)	25% s, 75% p	0 p	
3	3	3 sp^2 (trigonal planar)	33% s, 67% p	1 p	p_y p_z p_x
2	2	1 sp (linear)	50% s, 50% p	2 p	p_y, p_z

Pulling together the pieces of how to identify, define, and draw the fundamental structural features of organic molecules, there is a three-step hierarchy that can be followed. First: Identify the localized and delocalized electrons in the structure. Second: Assign the hybridizations. Third: Draw the 3D orbital picture with whatever labels are needed to define the bonding.

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Identifying localized and delocalized electrons. Your ability to assign hybridizations to atoms with confidence and then to draw accurate 3D orbital pictures rests completely on being able to identify the delocalizable and localized electrons associated with the atoms in a molecular structure; so be sure you are clear and confident about identifying, predicting, and drawing resonance contributors (Section 2.1). This ability is a critical prerequisite skill.

Assigning hybridizations. As seen in Figure 0235, the number of localized electron pairs also defines exactly the hybridization of that atom. Four localized electron pairs (covalent bonds and localized nbe) define the sp^3 hybridization; three localized electron pairs define sp^2 hybridization; and two localized electron pairs define sp hybridization.

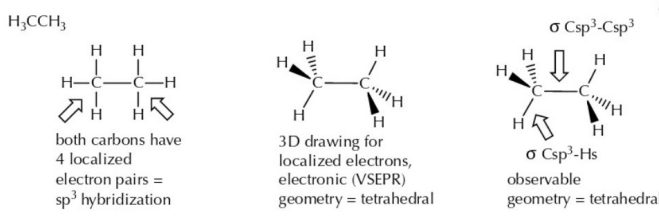
Drawing 3D orbital pictures. Once you have identified the hybridization, you can approach drawing a molecule in three stages. First: Draw the localized electron framework (see Figure 0230). Then, add in any unhybridized p orbitals that are needed on the sp^2 and sp atoms. Finally, add in the delocalizable electrons according to the resonance contributor that you are drawing. Up until the last step, the drawing is suitable for all resonance contributors.

Returning now to simple single, double, and triple bonding in hydrocarbons (see Figure 0225).

Ethane: H_3CCH_3 (Figure 0236). There are no delocalizable electrons (step 1). Both carbon atoms have 4 localized electron pairs, and so both are sp^3 hybridized (step 2). The electronic geometry for both carbons is tetrahedral, as is the observable geometry at both carbon atoms (step 3). There are 7 sigma (σ) bonds in the structure: 1 carbon-carbon v bond made from combining 2 sp^3 orbitals, and 6 carbon-hydrogen σ bonds made from combining a carbon sp^3 with a hydrogen s. The tetrahedral representation is used for both carbon atoms and the components of the bonds can be defined.

Figure 0236

Construction of a 3D orbital drawing for ethane (H_3CCH_3).


H3CCH3
both carbons have 4 localized electron pairs = sp3 hybridization
3D drawing for localized electrons, electronic (VSEPR) geometry = tetrahedral
σ Csp3-Csp3
σ Csp3-Hs
observable geometry = tetrahedral

The other two hybridizations include 1 to 2 unhybridized p orbitals. An unhybridized p orbital can be empty (as in the case of an open shell atom), filled by a delocalizable electron pair, or it can be sharing electrons with another p orbital that is parallel to it, which is called pi (π) bonding.

Ethene: H_2CCH_2 (Figure 0237). Ethene has 1 delocalizable electron pair, because of the double bond, and 5 localized pairs. Both of the carbons have 3 localized electron pairs, and so both are sp^2 hybridized. The electronic geometry for both carbons is trigonal planar, as is the observable geometry at both carbons atoms. There are 5 sigma bonds in the structure: 1 carbon-carbon sigma bond made from combining 2 sp^2 orbitals, and 4 carbon-hydrogen sigma bonds made from combining a carbon sp^2 with a hydrogen s.

Each of the sp^2 carbon atoms carries an unhybridized p orbital, and there will be a pair of electrons shared (delocalized) between these two carbon atoms by the pi bonding overlap of those two p orbitals when they are parallel to one another.

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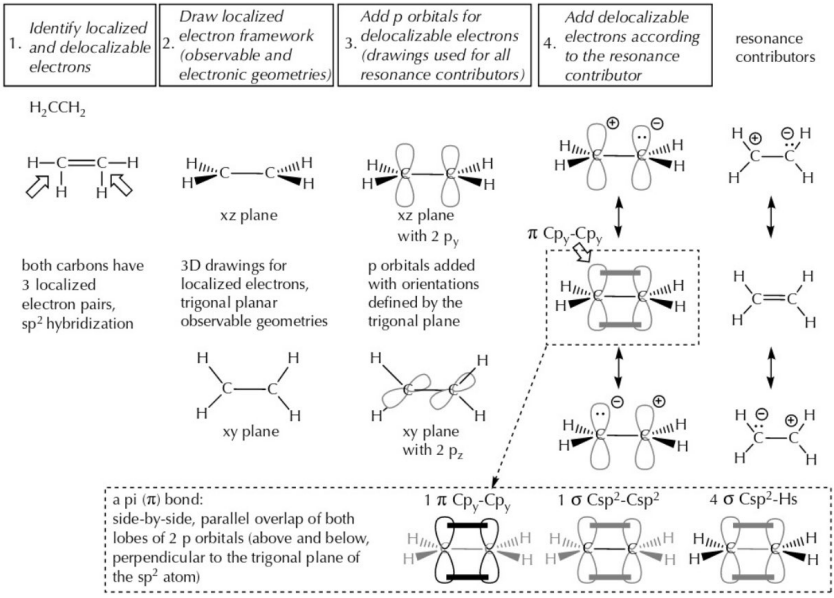
Because the two p orbitals need to be parallel for delocalization (sharing the pair of electrons), the corresponding trigonal planes of the two sp^2 carbon atoms need to be coplanar. If the two p orbitals are parallel and both oriented in the py direction, then the trigonal planar bonds need to be in the xz plane (perpendicular to the plane of the page or writing surface).

Alternatively, if the two p orbitals are aligned and both oriented in the pz direction, then the trigonal planar bonds need to be in the xy plane (the plane of the page or writing surface). By constructing the drawing as a process, you can (1) take the inventory of localized and delocalizable electrons using any of the resonance contributors; (2) draw the 3D localized electron framework; (3) lay in the unhybridized p orbitals, and you end up with a picture than can (and must!) work for all of the resonance contributors; and then (4) you make the commitment to add in the delocalizable electrons for the resonance contributor you are drawing.

The major resonance contributor for ethane has 1 pi (π) bond in addition to the 5 sigma (σ) bonds, while the minor contributors have two isolated p orbitals, one of which is full and the other of which is empty.

Figure 0237

Construction of a 3D orbital drawing for ethene (H_2CCH_2), including resonance contributors.


1. Identify localized and delocalizable electrons
2. Draw localized electron framework (observable and electronic geometries)
3. Add p orbitals for delocalizable electrons (drawings used for all resonance contributors)
4. Add delocalizable electrons according to the resonance contributor
resonance contributors
H2CCH2
both carbons have 3 localized electron pairs, sp2 hybridization
xz plane
3D drawings for localized electrons, trigonal planar observable geometries
xz plane with 2 py
p orbitals added with orientations defined by the trigonal plane
π Cpy-Cpy
xy plane
xy plane with 2 pz
a pi (π) bond: side-by-side, parallel overlap of both lobes of 2 p orbitals (above and below, perpendicular to the trigonal plane of the sp2 atom)
1 π Cpy-Cpy
1 σ Csp2-Csp2
4 σ Csp2-Hs

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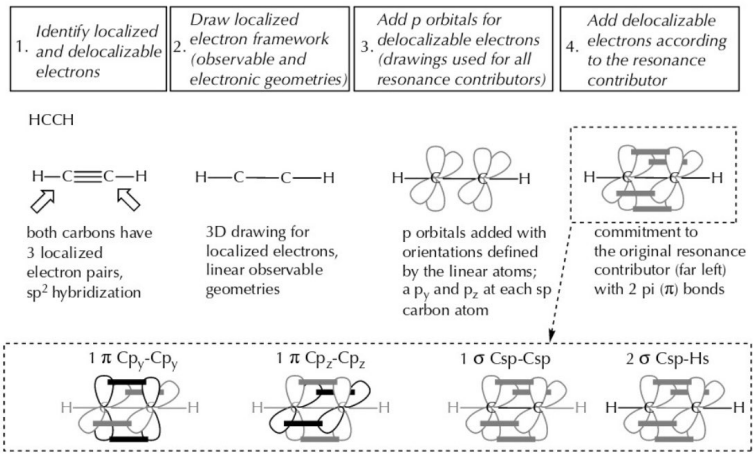
Ethyne: HCCH (Figure 0238). Ethyne has 2 delocalizable electron pairs because of the triple bond. Both of the carbon atoms have 2 localized electron pairs, and so both are sp hybridized. The electronic geometry for both carbons is linear, as is the observable geometry at both carbon atoms. There are 3 sigma bonds in the structure: 1 carbon-carbon sigma bond made from combining 2 sp orbitals, and 2 carbon-hydrogen sigma bonds made from combining a carbon sp with a hydrogen s. Each of the sp carbon atoms carries 2 mutually perpendicular unhybridized p orbitals, and there will be a pair of electrons shared (delocalized) between the 2 parallel orbital pairs, creating 2 perpendicular pi (π) bonds.

Figure 0238

Construction of a 3D orbital drawing for ethyne (HCCH).


1. Identify localized and delocalizable electrons
2. Draw localized electron framework (observable and electronic geometries)
3. Add p orbitals for delocalizable electrons (drawings used for all resonance contributors)
4. Add delocalizable electrons according to the resonance contributor
HCCH
H—C≡C—H
H—C—C—H
both carbons have 3 localized electron pairs, sp² hybridization
3D drawing for localized electrons, linear observable geometries
p orbitals added with orientations defined by the linear atoms; a p_y and p_z at each sp carbon atom
commitment to the original resonance contributor (far left) with 2 pi (π) bonds
1 π Cp_y-Cp_y
1 π Cp_z-Cp_z
1 σ Csp-Csp
2 σ Csp-Hs

Drawing more complex structures. Because the line, dash, and wedge notation uses the plane of the page (or writing surface) as a reference, drawings of more complex structures are inherently clearer and more comprehensible when as many atoms as possible are kept in the plane of the page. There are no standard conventions for how to draw a new 3D center when it is out of the writing surface (Figure 0239).

If you have a set of more than two sp^2 atoms, it is a generally recommended to keep the trigonal planes of those atoms in the plane of the writing surface if possible. The figure includes an attempt to adapt the conventional notation to place the trigonal planes in the yz plane, and the effect on drawing a set of other sp^2 atoms as well as an sp^3 atom that are not located in the xy plane of the writing surface. These sorts of artistic interpretations have no fixed conventions, and so they are discouraged.

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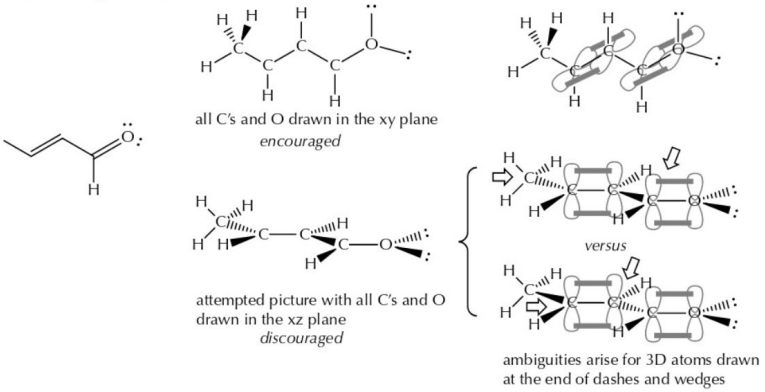
Figure 0239

Drawings are more clear when more atoms are in the xy plane (the writing surface).


all C's and O drawn in the xy plane
encouraged
attempted picture with all C's and O drawn in the xz plane
discouraged
versus
ambiguities arise for 3D atoms drawn at the end of dashes and wedges

Some more sophisticated examples are shown in Figure 0240. The drawings are developed using the same sequence: identification of the delocalizable and localized electrons, assignment of hybridizations based on number the localized electron pairs, drawing the localized electron framework, laying in the unhybridized p orbitals, and adding in the delocalized electrons according to the selection of which resonance contributor is being represented.

In the third example in the figure, two different resonance contributors are shown. As described earlier, the localized electron frameworks and the set of p orbitals are identical, as they must be, for resonance contributors. Drawings for resonance contributors only differ according to the specific distribution of the delocalizable electrons in that particular contributor. The orbital diagrams provide a way to better visualize for the redistribution of electrons as indicated by the curved arrow notation. In Figure 0241, the drawings are identical to some of those in Figure 0240, but now include the curved arrows.

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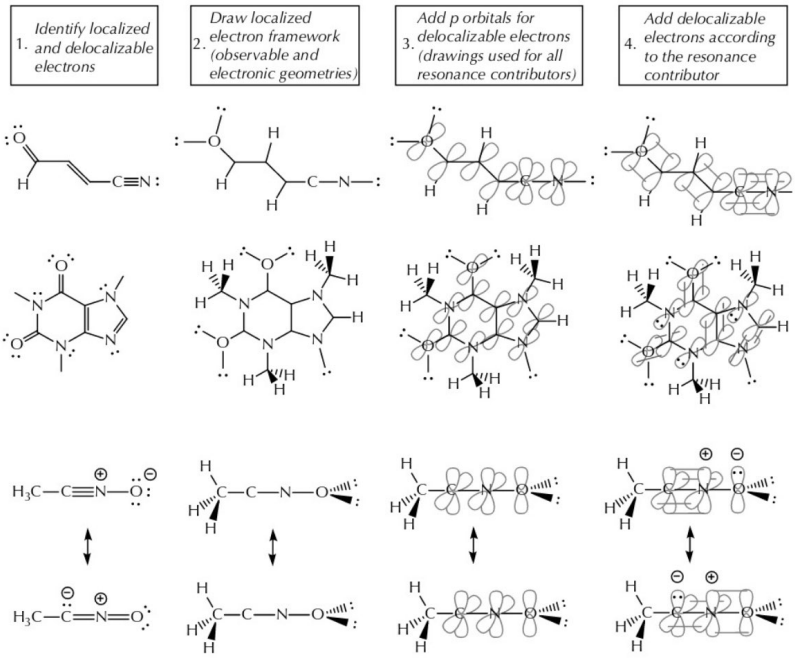
Figure 0240

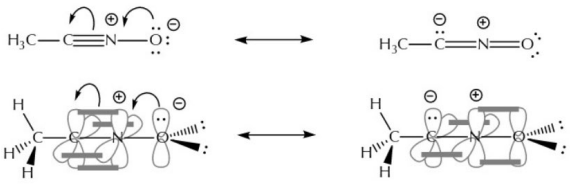
Constructing 3D orbital drawings.


1. Identify localized and delocalizable electrons
2. Draw localized electron framework (observable and electronic geometries)
3. Add p orbitals for delocalizable electrons (drawings used for all resonance contributors)
4. Add delocalizable electrons according to the resonance contributor

Constructing 3D orbital drawings: localized electron framework followed by p orbitals, followed by the delocalized electrons committed to one resonance contributor.

Figure 0241

Comparing the relationship between resonance contributors using Lewis structures and 3D orbital drawings when using the curved arrow notation.



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PRACTICE QUESTIONS

2.06 Provide the 3D orbital drawings for the following molecules (use the resonance contributor shown in the question). Use lines, dashes, and wedges to represent sigma bonds and the directionality of localized electron pairs. Use p orbitals for delocalizable electrons (pi bonds, nonbonding electron pairs) or leave empty if representing an open shell atom. Identify the anticipated observable geometry for all non-hydrogen atoms (or indicate that it is not observable).

(a) water

observable geometries:

(b) hydrocyanic acid

H–CN

observable geometries:

(c) dichloromethane

CH_2Cl_2

observable geometries:

(d) acetone

observable geometries:

(e) propyne

$H–C{\equiv}C–CH_3$

observable geometries:

(f) nitroxyl

HNO

observable geometries:

(g) dibromine monoxide

BrOBr

observable geometries:

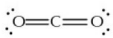
(h) ethylene oxide

observable geometries:

(i) carbon monoxide

observable geometries:

(j) carbon dioxide



observable geometries:

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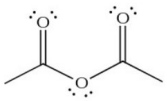
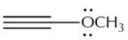
2.07 Provide the 3D orbital drawings for the following molecules (use the resonance contributor shown). Use lines, dashes, and wedges to represent sigma bonds and the directionality of localized electron pairs. Use p orbitals for delocalizable electrons (pi bonds, nonbonding electron pairs) or leave empty if representing an open shell atom. Identify the anticipated observable geometry for all non-hydrogen atoms (or indicate that it is not observable).

(a) acetic anhydride

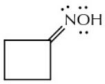


(b) methoxyborane

(c) methoxyethyne



(d) cyclobutanone oxime



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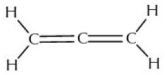
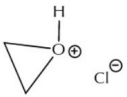
2.07 (cont.)

(e) benzene

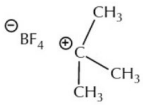
(f) allene



(g) oxiranium chloride



(h) 2-methyl-2-propanylium tetrafluoroborate



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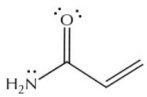
2.08 For each of the following molecules:
I. Identify the delocalizable electrons with an asterisk (*) and define the hybridizations for all non-hydrogen atoms
II. Draw a representation for the 3D geometry of the localized electron framework
III. Redraw II and add the required p orbitals in the proper 3D orientation
IV. Redraw III and add the delocalizable electrons according to the original contributor in I

(a) methacrylamide (forms the cement used to bond bone replacements to bone)

I.



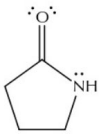
II.

III.

IV.

(b) 2-pyrrolidone (used in inkjet cartridges)

I.



II.

III.

IV.

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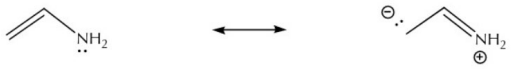
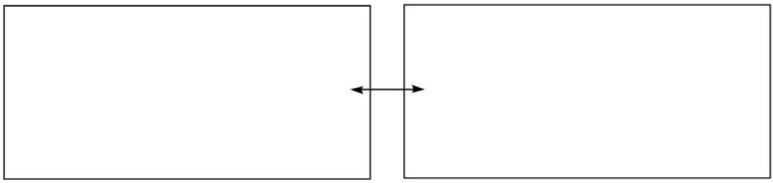
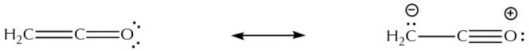
2.09 Provide the 3D orbital drawing for each member of the following pairs of resonance contributors. Include the curved arrow notation that indicates the relationship between the two contributors on your 3D drawings.

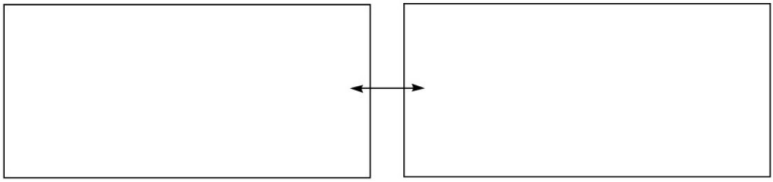
(a)



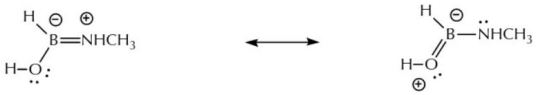


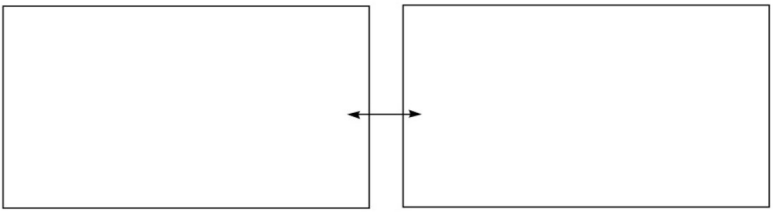
(b)





(c)





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2.3 Bonded and Nonbonded Structure and Properties

A. Bond Lengths

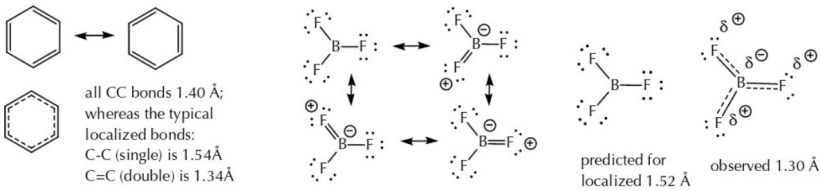
Another outcome from x-ray crystallography (Section 2.2A) in the early 1900s, and then from microwave spectroscopy in the 1940s, was the ability to measure bond distances in molecules. This level of information about molecules was previously unavailable. These measurements have led to generalizations about how differences in atomic properties, such as electronegativity or delocalization of electrons, affect bond lengths.

Bond distance measurements are important to structural theory. Because electrons cannot be located by experiment, the predictions from electron delocalization (for example) are strongly supported by being able to measure the distance between atoms. These bond distance observations do not prove anything about delocalization of electrons, but they build a strong and self-consistent picture that supports the idea.

Experimentally, the fact that benzene (Figure 0242) is a perfect hexagon with six equal bond lengths whose distance is about halfway between traditional single and double bonds gives a great deal of support to the delocalization model. The data for the boron-fluorine bond in BF_3, in which the three BF bonds in BF_3 are shorter than might be expected, is consistent with delocalization and the significance of closed shell resonance contributors (Figure 0242).

Figure 0242

Bond distances add strong support for the electron delocalization model.


benzene
trifluoroborane
all CC bonds 1.40 Å; whereas the typical localized bonds: C-C (single) is 1.54Å C=C (double) is 1.34Å
predicted for localized 1.52 Å
observed 1.30 Å

The following four generalizations are ranked according to their degree of significance as applied to predicting the rank order of bond lengths when considering the molecular structures built from the main group organic elements. While the diversity in molecular structures means that exceptions are always possible, these factors, in this order, are a good starting point in the absence of experimental data that might contradict the generalization.

Bond Length Generalization 1: Atom size differences based on period (row). Atom size increases as you move down a column on the periodic table. The most significant atom size differences, and therefore bond length differences, are seen when comparing atoms in different rows of the periodic table. To use an analogy, the distance between the centers of two side-by-side basketballs (two carbon atoms) can never be as close as the centers of a basketball that is side-by-side with a baseball (a carbon atom and a hydrogen atom), meaning that covalent bonds involving hydrogen atoms and any other atoms will be shorter than bonds between those other atoms themselves (Figure 0243). Similarly, one would expect any carbon-sulfur bond to be longer than any carbon-carbon bond, regardless of whether there is multiple bonding or not.

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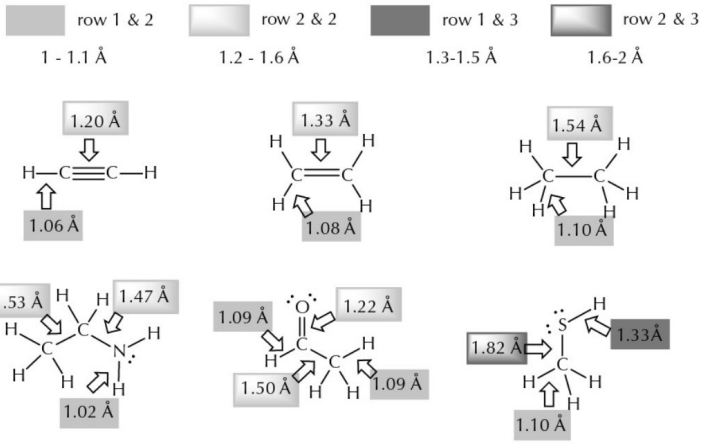
Figure 0243

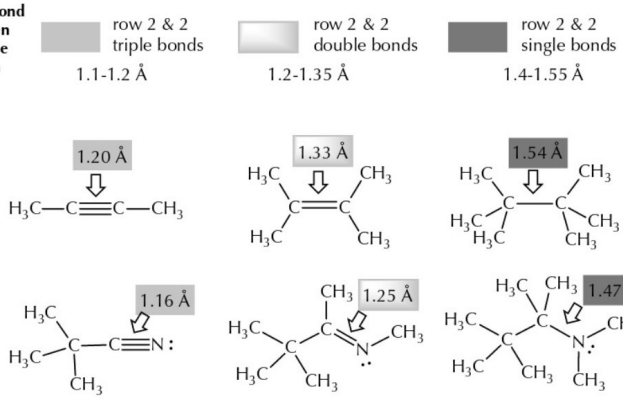
Comparison of bond distances between atoms in different rows versus in the same row of the periodic table.



Bond Length Generalization 2: Bond order within the same row. Within the atoms of the same row, triple bonds are shorter than doubles bonds, which are both shorter than single bonds. The more negative electrons there are between two positive nuclei, the closer those nuclei can be. And although there are small differences in atomic size for atoms in the same row, based upon electronegativity (see the next generalization), bond order (shortest to longest: triple, double, single bonds) is the next most significant factor in determining bond length (Figure 0244). A carbon-carbon triple bond is shorter than a carbon-oxygen double bond, but none of these multiple bonds can be shorter than the carbon-hydrogen bond.

Figure 0244

Comparison of bond distances between atoms in the same row that differ in bond order.



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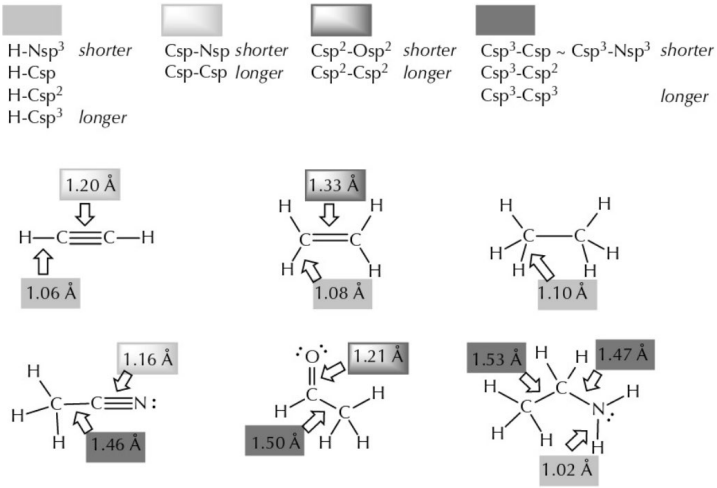
Bond Length Generalization 3: Electronegativity reduces atomic size, affecting distance within comparable bond orders. As the number of protons in the atomic nucleus increases (going left to right within a row on the periodic table), the increasing positive charge overcomes the added electron-electron repulsion, and the atomic radius decreases slightly. This attraction by the increasing positive nuclear charge for electrons is the origin of the property we call electronegativity. Electronegativity provides a small contraction of the atomic radius, and so shortens slightly the bond distance when only electronegativity is the difference.

Because hybridization is also a fundamental difference in the proximity of electrons to the nucleus, hybridization differences also represent differences in electronegativity. That is, an sp-hybridized atom has 50% s character, and holds its localized electrons closer to the nucleus. An sp-hybridized atom is more electronegative than its sp^2-hybridized counterpart (33% s character), which is in turn more electronegative than the sp^3-hybridized atom (25% s character) as shown in Figure 0245.

Figure 0245

Comparison of bond distances between atoms in the same row, in the same bond order, that differ in electronegativity, including hybridization.



Bond Length Generalization 4: electron delocalization affects bond distances, resulting in partial bonds that can lengthen or shorten distances, more or less, according to the significance of the resonance contributors. Because actual bond lengths are not limited to integers, the effects from electron delocalization occur over the range of possible bond orders. Predicting the effects of resonance contributors on bond lengths relies on the assessment of their relative importance (Figure 0246).

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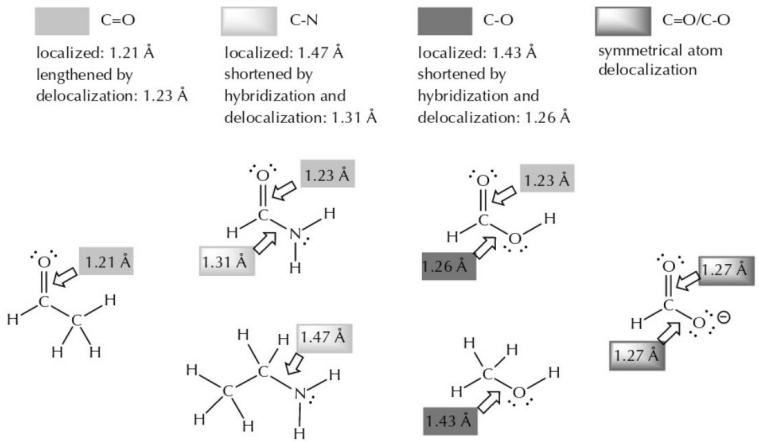
Figure 0246

Comparison of bond distances between atoms in cases where there are effects from electron delocalization.



It is important to note that when all of these generalizations are operating in the same molecular structure, the criteria can overlap, and you may not be able to make an absolute prediction about the ranking of every bond distance. Carbon-hydrogen bonds at carbons with the same hybridization might differ, in fact, but the difference will be quite small and unpredictable. As is so often true in science, the generalizations will work in lots of cases and enable you to make predictions, but there will also be times where they fail, where they cannot resolve conflicting criteria, and where only the experimental result can provide the final resolution to a debate.

B. Van der Waals Interactions: London Dispersion Forces and Induced Dipoles

Substances that are made up of individual atoms have very few forces holding collections of them together, and they have correspondingly low boiling points. That is, the interatomic force that needs to be overcome to get a collection of them, in the liquid phase, to separate into the gas phase is quite low. Helium has a boiling point of only about 4 K (4 degrees above absolute zero), and neon has a boiling point of 27 K. Methane (CH_4), whose mass (16 g/mol) is actually less than neon (20 g/mol), and is a perfectly nonpolar tetrahedron, has a considerably higher boiling point (112 K). There are intermolecular interactions that can take place between even small, nonpolar molecules that are not available to atoms. And as we look at the simplest hydrocarbons, their boiling points increase significantly with each added carbon, implying a large increase in intermolecular forces that need to be overcome (ethane, CH_3CH_3: 184 K; propane, $CH_3CH_2CH_3$: 232 K, -44 °C; butane, $CH_3CH_2CH_2CH_3$: 272 K, -1 °C; pentane, $CH_3CH_2CH_2CH_2CH_3$: 309 K, +36 °C). Again, as a comparison, the last example in that short series, pentane, has a mass of 72 g/mol, and a boiling point of 309 K, while the nearest noble gas to that mass, krypton (84 g/mol), has a boiling point of 120 K, just barely higher than methane.

What intermolecular forces are holding these nonpolar organic molecules together in the liquid phase? In the single, spherical atoms of helium and neon, the electrons are more or less symmetrically surround-

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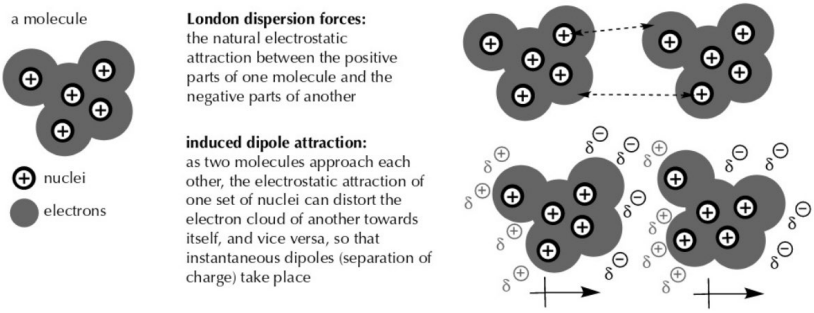
ing the nuclei, and the single center of positive charge is sitting exactly where the single center of negative charge is located. Molecules, on the other hand, rely on bonding (intramolecular forces) to maintain their structures, and bonding is built upon the basic physics of electrostatic attraction of opposite charges. Intermolecular forces are weaker versions of exactly the same thing, as the positively charged portions of one molecule (the nuclei) are attracted to the negative charged portions of another (the electrons). Even in molecules that are quite nonpolar, such as hydrocarbons, favorable intermolecular electrostatic forces cause attractive interactions between molecules, and this affects their properties (such as boiling point). In methane, however, there are multiple nuclei with different distributions of electrons surrounding them. It is more likely, in methane than in neon, that one of the five nuclei in one methane molecule might be slightly attracted by the electrons of another methane, than in the comparable neon-to-neon situation.

The electrostatic attractive forces between molecules are collectively referred to as van der Waals interactions. For nonpolar molecules, like methane, which do not have bonds with large differences in electronegativity that result in significant partial charges, the van der Waals interactions are the simple electrostatic attraction that can exist between molecules (London dispersion forces), where the electrons from one molecule are attracted to the nuclei of another. These forces include attractions that result from the natural asymmetries in electron density that occur in molecules, as well as the asymmetries that result when one molecule causes (induces) the asymmetry (a dipole) in another (Figure 0247).

In Figure 0247, a nonpolar molecule is represented as a gray cloud of negatively charged electrons in which the positively charged nuclei are sitting. The molecule itself hangs together because the electrons (in bonds) allow the nuclei to overcome their natural repulsion. On the left-hand side of the figure, London dispersion forces are represented, as the positive nuclei from one molecule are also attracted to the electrons of another molecule, creating an attractive intermolecular force. On the right-hand side of the figure, as two nonpolar molecules approach one another, the illustration suggests that the electrons are not rigidly fixed around their nuclei, and that the net distribution of electrons around the nuclei can be distorted, or polarized, as two molecules approach one another. Not only are there London dispersion forces acting between the molecules, but the distortion of the electron clouds creates a temporary, instantaneous dipole moment in the otherwise nonpolar molecule, and these instantaneous dipoles, as temporary magnets, can lead to additional intermolecular attraction.

Figure 0247
London dispersion forces and induced dipoles.


a molecule
nuclei
electrons
London dispersion forces: the natural electrostatic attraction between the positive parts of one molecule and the negative parts of another
induced dipole attraction: as two molecules approach each other, the electrostatic attraction of one set of nuclei can distort the electron cloud of another towards itself, and vice versa, so that instantaneous dipoles (separation of charge) take place

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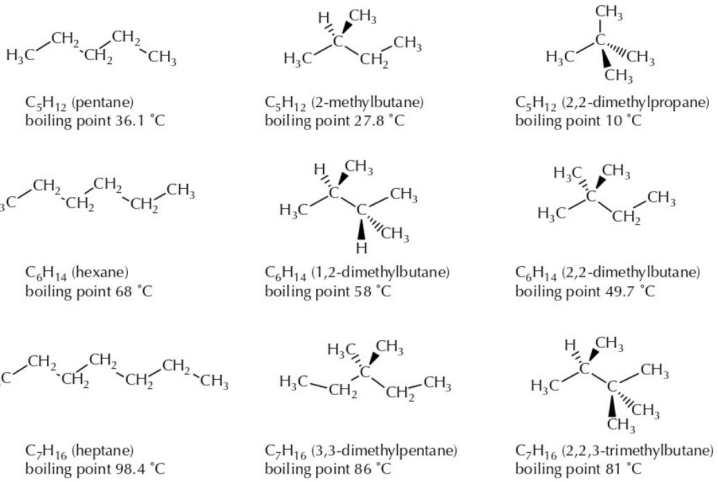
For structural isomers (same atoms, same mass) with different shapes, the more linear molecules have a greater opportunity for surface area contact, which increases the opportunity for intermolecular forces along their surfaces, while more branched or spherical shapes provide less contact. In general, the more linear isomers have higher boiling points, for example, than their branched counterparts (Figure 0248). The collective effect from London dispersion forces can be large, because every part of the molecule is involved, so the increase in boiling points as the number of atoms in a chain grows is consistent with these increased forces that need to be overcome.

Figure 0248

Overall structural shape influences boiling point by how effectively the molecules can experience intermolecular interactions.



C. Van der Waals Interactions: Permanent Dipole-Dipole

Molecules with highly polar covalent bonds can have relatively strong and permanent dipole moments. A collection of molecules with permanent dipoles is analogous to having a collection of small magnets thrown together. The molecules are imagined to orient themselves in such a way that electrostatic attraction of the opposite partial charges takes place (dipole-dipole attraction). The dipole-dipole attraction needs to be overcome if the molecules are to be separated from one another (again, as in boiling, going from the liquid to the gas phase). Molecules can have highly polar bonds (bond dipoles) that are held by molecular geometries in a way where the net molecular dipole moment is zero, which does not provide for molecular dipole-dipole attraction. In Figure 0249, the carbon-halogen bonds are fixed by the carbon-carbon double bond to be held in the same direction (called *cis* in the name), resulting in a molecular dipole moment, or in the opposite direction (*trans*), where the bond dipoles cancel one another, resulting in no molecular dipole moment.

The data on the series of compounds in Figure 0249 also provides a terrific reminder that there is never just one factor involved in explaining differences in properties and reactivity. As you move from the dichloroethenes to the diiodoethenes, the overall dipole moment in the *cis* isomer decreases, although the boiling points are increasing steadily. The more electronegative chlorine atoms, where the electrons are

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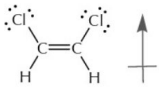
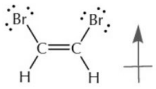
closer to the nuclei, create a more polar bond and a higher dipole moment. On the other hand, the electrons around the iodine nuclei are less tightly held, more likely to be polarized, and lead to higher London forces. The difference in boiling points associated with the dipole moment is most significant for the dichloroethene isomers. But by the time you reach the diiodoethenes, the effect of the dipole moments appears to be overwhelmed by factors that are starting to reverse the correlation with geometry! The *trans* compound has a slightly higher reported boiling point. This is not a contradiction to the effects of the dipole moment, but an indication that the dipole effects are competing with something else. What is it? Experimentally, it is impossible to tell, but we might speculate that the London dispersion forces in the *trans* isomer are greater than in the *cis* isomer because both of the highly polarizable iodine atoms are more independently exposed to other molecules in the *trans* arrangement. Or some other reason. All we have are the experimental boiling points, and these aggregate every effect.

Figure 0249

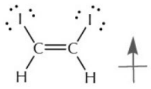
Dipole-dipole interactions influence boiling point by increasing intermolecular interactions.



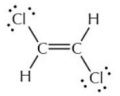
$C_2H_2Cl_2$
(*cis*-1,2-dichloroethene)
Dipole moment 1.9 D
boiling point 60.2 °C



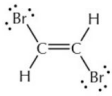
$C_2H_2Br_2$
(*cis*-1,2-dichloroethene)
Dipole moment 1.22 D
boiling point 112 °C



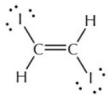
$C_2H_2I_2$
(*cis*-1,2-diiodoethene)
Dipole moment 0.75 D
boiling point 188 °C



$C_2H_2Cl_2$
(*trans*-1,2-dichloroethene)
Dipole moment 0 D
boiling point 48.5 °C



$C_2H_2Br_2$
(*trans*-1,2-dichloroethene)
Dipole moment 0 D
boiling point 108 °C



$C_2H_2I_2$
(*trans*-1,2-diiodoethene)
Dipole moment 0 D
boiling point 191 °C

D. Hydrogen Bonding

Hydrogen atoms are limited to having a duet (a pair) of valence shell electrons to achieve the closed shell electron configuration of helium ($1s^2$). If a covalent bond involving a hydrogen atom is highly polarized due to electronegativity differences, then the only electrons associated with the hydrogen atom are being pulled away from it. Using a simple way of thinking about that idea, it means that the hydrogen atom does not have its full duet of electrons, and its positively charged nucleus is being exposed as another nucleus pulls its electrons away.

The partially positively charged, electron-poor hydrogen atom with its exposed nucleus is equivalent to a partially open shell at the hydrogen atom. Another type of intermolecular force is conceived of as a second atom using a nonbonding electron pair to share some electron density with these electron-poor hydrogen atoms. The intermolecular association between electron-poor hydrogen atoms and the electron-rich atom with its nonbonding electron pair is called a hydrogen bond (Figure 0250). The partner with the electron-poor hydrogen atom is called the hydrogen bond donor, while the partner bearing the atom with a nonbonding electron pair to share is called the hydrogen bond acceptor. Note the unfortunate shift in language as an atom-centered model is contrasted with an electron-centered model: the atom that is a hydrogen bond acceptor is the electron pair donor.

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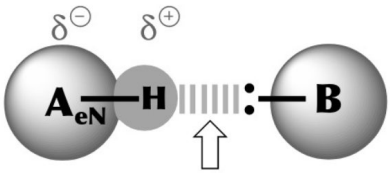
Figure 0250

General picture of a hydrogen bond and its defining partners.

Hydrogen Bond Donor
polar covalent bond involving a hydrogen atom (eN = electronegative)

Hydrogen Bond Acceptor
atom with a nonbonding electron pair to share with the electron-poor H atom



"hydrogen bond" intermolecular interaction

Water is the molecule typically used in general chemistry to illustrate both hydrogen bonding and dipole-dipole attraction as intermolecular forces. The comparison between methane (CH_4), ammonia (NH_3), and water (H_2O) is particularly informative. A property called the kinetic volume of a molecule can be measured; this value gives the effective surface area of the molecule when they are undergoing collisions. The kinetic volumes for these three molecules are 29 Å^3 (methane), 11 Å^3 (ammonia), and 10 Å^3 (water). Although the masses of these three compounds are comparable, methane has more atoms and is more naturally larger, and it should accordingly have higher London dispersion forces than either ammonia or water. In contrast, ammonia and water are about the same size, so the difference in boiling points between these three can give an idea of whether size alone is making a difference. And indeed, these three molecules have distinctively different boiling points (methane: 112 K; ammonia: 240 K; water: 371 K), so intermolecular attractive forces above and beyond London dispersion forces are needed to explain these differences.

Methane (CH_4, molecular weight 16 g/mol) and ammonia (NH_3, 17 g/mol) have nearly the same mass as water (H_20, 18 g/mol). Methane in made up of nonpolar CH bonds and it is a perfectly symmetrical tetrahedron with a molecular dipole moment of 0 Debye; its boiling point is –161.5° (111.7 Kelvin, temperature above absolute zero, which exemplifies the importance of London dispersion forces, as described earlier, even in such a small and symmetrical molecule). Ammonia has an asymmetrical trigonal pyramidal structure that creates a permanent dipole moment, which is observed to be 1.46 Debye. The boiling point of ammonia (-33.4 °C, 239.8 K) is over 100 degrees higher than methane, which is evidence for needing to overcome the intermolecular dipole-dipole interactions.

The OH bonds in water are more polar than either CH or NH bonds because of the higher electronegativity of oxygen, and the bent geometry results in a molecular dipole moment of 1.85 Debye, larger but ultimately comparable to that of ammonia. The magnitude of the boiling point of water (100 °C, 371.2 K), relative to ammonia, is difficult to explain on the basis of only the dipole-dipole attraction. The added interaction of hydrogen bonding between the molecules of water is used to explain this relatively high boiling point (Figure 0251).

Liquid water is a perfect storm of hydrogen bonding: each molecule of water has two hydrogen bond donor sites and two hydrogen bond acceptor sites, and this aggregate collection of intermolecular interactions needs to be overcome to get water from the liquid phase into the gas phase. By the middle of the 20th century, direct experimental evidence emerged for the arrangement of the atoms in solid water (ice). As the x-ray crystallographer, William H. Zachariasen, wrote in 1935, "[between two water molecules, we observe that] every hydrogen atom is thus linked to two oxygen atoms; undoubtedly it is linked more

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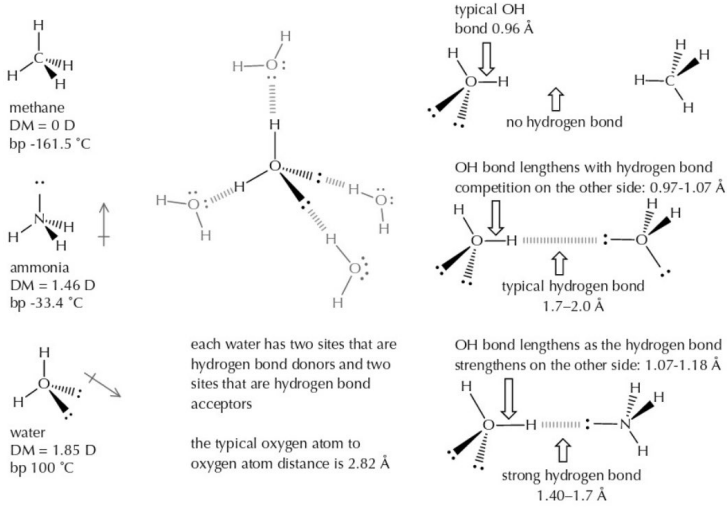
strongly to one of the oxygen atoms than to the other." The significance of hydrogen bonding is reflected in the physical properties of compounds in which such bonding occurs, and no less so than in water. Hydrogen bonding, for example, is responsible for the form of ice crystals, resulting in a lower density for ice than for liquid water. (Ice floats in water, a property that has profound consequences in nature. Imagine a lake freezing from the bottom up!)

Figure 0251

Hydrogen bonding in water is used to explain its unexpectedly high boiling point relative to ammonia and methane.


methane
DM = 0 D
bp -161.5 °C
ammonia
DM = 1.46 D
bp -33.4 °C
water
DM = 1.85 D
bp 100 °C
each water has two sites that are hydrogen bond donors and two sites that are hydrogen bond acceptors
the typical oxygen atom to oxygen atom distance is 2.82 Å
typical OH bond 0.96 Å
no hydrogen bond
OH bond lengthens with hydrogen bond competition on the other side: 0.97-1.07 Å
typical hydrogen bond 1.7–2.0 Å
OH bond lengthens as the hydrogen bond strengthens on the other side: 1.07-1.18 Å
strong hydrogen bond 1.40–1.7 Å

As seen in Figure 0250, the attractive force of a hydrogen bond is conventionally drawn using a hashed line rather than the solid line used for a covalent bond. Although hydrogen bonding is the strongest known type of intermolecular interaction, it is still much weaker than a chemical bond. Hydrogen bonds are interactions between molecules and should not be confused with covalent bonds to hydrogen within a molecule. Even in water, where the covalent OH bond can break with a high frequency (the acid-base reaction between $H_2O + H_2O$ to give hydronium ion, H_3O^+, and hydroxide ion, HO^-), the association and dissociation that forms and breaks the hydrogen bonding interaction happens about 1016 times for each time one of the covalent bonds breaks.

A few more experimental facts about hydrogen bonding in water are shown in Figure 0251. As might be anticipated, as a hydrogen bond forms, the covalent bond involving the hydrogen bond donor lengthens (weakens) when the hydrogen atom begins to share electron density with the hydrogen bond acceptor (the electron pair donor). When a molecule, such as water, possesses multiple sites for being a hydrogen bond donor (2 OH bonds) or a hydrogen bond acceptor (2 nbe pairs on O), the normal expectation is that there will not be more than one hydrogen bond interaction between any two partners. The center image in Figure 0251 is consistent with that principle. While the centrally located water molecule is shown with four hydrogen bonds, four different molecules are required to form them. It is quite possible for two different partners to share more than one hydrogen bond (for example, base pairing in DNA), but

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it is best to have experimental information to use before making that proposal. In the absence of experimental data, or explicit guidance, the default assumption is for one hydrogen bond between any given donor-acceptor pairing.

Predictable hydrogen bonds involving uncharged atoms. Based on experiment, there are a few generalizations about predicting when a hydrogen bond will be possible.

Forming significant hydrogen bond donors is predictable when hydrogen atoms are covalently bonded to nitrogen, oxygen, or fluorine atoms (N-H, O-H, F-H). And comparably, the nonbonding electron pairs on nitrogen, oxygen, or fluorine atoms can serve predictably as hydrogen bond acceptors (N:, O:, F:). Other bonds involving hydrogen atoms can be donors, and other atoms can be acceptors, but not as predictably, so experimental evidence is needed.

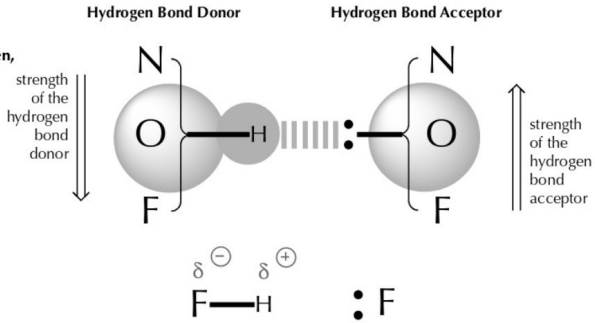
Atom size appears to make a difference. Even though chlorine has the same electronegativity as nitrogen, uncharged chlorine atoms are not significantly involved in hydrogen bonding. Chlorine, in the third period of the periodic table, has larger atoms than those of fluorine, oxygen, or nitrogen (the chlorine atom radius is 1.75 Å, while the fluorine, oxygen, and nitrogen atoms are 1.47, 1.52, and 1.55 Å, respectively). We imagine that the valence electrons on a chlorine atom are more diffuse and are not shared with the small hydrogen atom (radius 1.20 Å) as effectively.

Electronegativity differences play a role, too. Hydrogen atoms bonded to carbon are not predictably involved in the formation of hydrogen bonds because the bond polarity is too low. Again, this does not rule out CH bonds as hydrogen bond donors, but, as stated above, experimental evidence for a phenomenon is all that is needed to support an argument for a counterexample to the N/O/F generalizations.

Figure 0252 summarizes nine pairings of hydrogen bond donors with hydrogen bond acceptors that are formed predictably. The higher electronegativity of fluorine makes the HF bond the most polar, and so the best hydrogen bond acceptor in this group. The same electronegative property of fluorine means that its atoms are less likely to share their electrons with another atom, and so, for the same reason, it is the poorest hydrogen bond acceptor.

Figure 0252

Hydrogen bonds form predictably when the donors and acceptors involve nitrogen, oxygen, and fluorine atoms.



best hydrogen bond donor from this list, the electronegativity of the fluorine means that it does not share its electrons with the H atom to which it is bonded, and makes the hydrogen an electron-poor atom

poorest hydrogen bond acceptor from this list, the electronegativity of the fluorine means that it does not share its electrons with an external hydrogen that is seeking electrons

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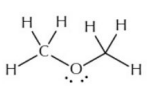
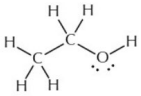
The effect of hydrogen bonding is also demonstrated dramatically by the difference in the boiling points of ethanol, CH_3CH_2OH, and its isomer, dimethyl ether, CH_3OCH_3. Ethanol is an alcohol. An alcohol resembles a water molecule in which a nonpolar hydrocarbon group has replaced a hydrogen atom. The polar part of the molecule is the hydroxyl group, OH (Figure 0253).

The hydrogen bonding that takes place between molecules of ethanol contributes to a much higher boiling point for this compound than that of dimethyl ether, in which the molecules are held together by only van der Waals and dipole-dipole interactions. The dimethyl ether molecule, which is exactly the same set of atoms, does not possess a hydrogen bond donor.



dimethyl ether
C_2H_6O
DM 1.30 D
bp -24 °C



ethanol
C_2H_6O
DM 1.69 D
bp 78 °C

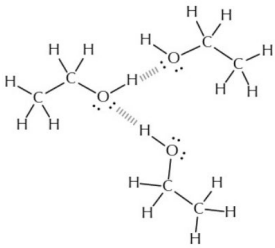


Figure 0253
Hydrogen bonding is used to explain the difference in boiling points between the two C_2H_6O structural isomers, ethanol and dimethyl ether.

Based on the generalizations above, as you move away from the second row elements, the effect from hydrogen bonding is predicted to diminish. Compare the boiling points of water (H_2O, 18 g/mol, boiling point 100 °C; DM 1.85 D) with the molecularly comparable hydrogen sulfide (H_2S, 34 g/mol, boiling point -62 °C; DM 0.97 D), where London dispersion forces are expected to be greater, but where the observed boiling point is 160 °C less than water. Hydrogen bonding is not predicted to be significant in hydrogen sulfide. Sulfur is a large atom, and so poorer at being a hydrogen bond acceptor, and the electronegativity of sulfur (2.58, Pauling scale) is nearly identical to carbon (2.55), so the S-H bond is not anticipated to be a good hydrogen bond donor.

Water is a major constituent of our surroundings and in living organisms, so an understanding of its chemistry is important. Water solubility plays a critical role in every aspect of biochemistry, where huge organic molecules and aggregates of organic molecules, from proteins to blood cells, need to operate.

One of the key properties of water is that it minimizes its surface area when exposed to nonpolar surfaces. For instance, small volumes of water form beads and droplets rather than simply spreading out. Without getting into the deep theory, water molecules at the surface interface of a nonpolar medium, such as air, hydrocarbons, or metal (i.e., the surface of a raindrop), are less stable than water molecules on the interior (called the bulk, which is any magnitude of material in three dimensions), where any given water molecule is completely encapsulated by other water molecules. The take-away message, for now: Water minimizes its interaction with nonpolar surfaces because the water molecules at the surface interface are less stable than in the bulk.

The solubility of organic molecules in water is a relevant topic to this subject. Hydrocarbons and other highly nonpolar molecules do not dissolve to any appreciable extent in water, and "oil and water do not mix" is a familiar saying.

We can dig a little deeper into this solubility phenomenon than just this saying. From a molecular perspective, when hydrocarbons are inserted into water, a new surface forms within the interior bulk of

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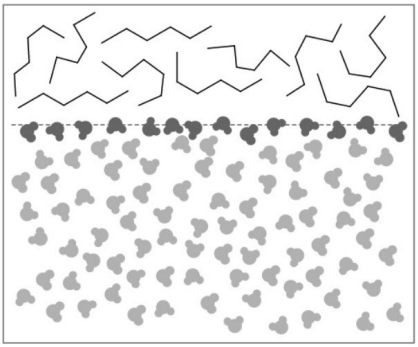
water, and the formation of these new surfaces is unfavorable. Consequently, even after they are mixed vigorously, hydrocarbons and water spontaneously separate from each other, as this minimizes the surface area of water (Figure 0254). In the left-hand image, a hydrocarbon is forcibly mixed into the water, and from a mixing point of view, this is good for the hydrocarbon. But from the perspective of the water, every single hydrocarbon molecule inserted into the bulk of water causes a great number of water molecules to form a new surface, surrounding the hydrocarbon, which has no ability to form hydrogen bonds or otherwise interact with the water. The increase in the unstable (darker gray) water molecules is illustrated. In the right-hand image, the water and hydrocarbon molecules have spontaneously separated, layered according to their density, and minimized the surface waters that are needed, creating a more stable overall situation.

Figure 0254

Water minimizes its surface area, and so nonpolar molecules that cannot interact with water will spontaneously separate, even after physical mixing takes place.

After physically mixing the nonpolar hydrocarbon hexane ($CH_3CH_2CH_2CH_2CH_2CH_3$) with water, there are lots of water molecules that end up forming new surfaces (darkened waters with dotted lines) in the interior bulk of the liquid water, and this is unfavorable.



The hexane and water molecules will spontaneously separate to minimize the amount of surface area contact (darkened waters with dotted line) between water molecules and the nonpolar hexane molecules. The hexane is therefore nearly completely insoluble in water.

Some organic molecules are quite soluble in water, and hydrogen bonding is important in determining their solubility. The part of an organic molecule that can participate in hydrogen bonding mimics the action of water and does not require a new surface to form. Commonly, part of the organic molecule interacts favorably with water (hydrophilic: water-loving) and part of it interacts unfavorably (hydrophobic: water-fearing). Molecules with a hydrophilic group, that can participate in the formation of hydrogen bonds with water, will dissolve in water if the nonpolar part of the molecule (the hydrophobic part, made up of carbon and hydrogen alone) is not too large. The favorable hydrogen bonding with one end of the molecule can counteract the formation of the new surface at the other end. For example, the solubilities in water of three alcohols—ethanol, 1-butanol, and 1-hexanol—vary with the size of the nonpolar portion of their molecules. The interaction between a dissolved species and the molecules of a solvent is known as solvation (Figure 0255).

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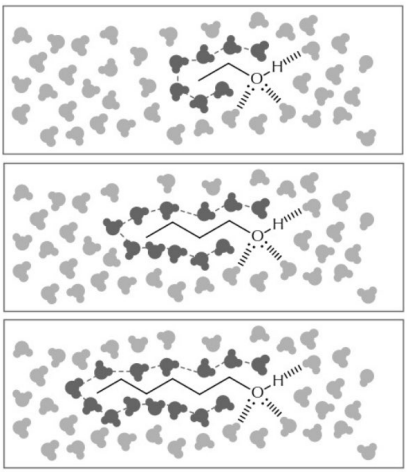
Figure 0255

Solvation of organic molecules via hydrogen bonding contributes to their water solubility.



ethanol in water
solubility: miscible (soluble in all proportions)

hydroxy group is hydrogen bonded with water, and overcomes the negative effect of the new surface waters (darkened/dotted) around the nonpolar hydrocarbon group

1-butanol in water
solubility: 0.11 mol/100 g water

hydroxy group is hydrogen bonded, and the negative effect of the new surface is proportionately larger than in ethanol, lowering the overall solubility

1-hexanol in water
solubility: 0.0058 mol/100 g water

hydroxy group is hydrogen bonded, and the negative effect of the new surface is now dominating; adding 2 more carbons and the organic molecule is insoluble

The overall solubility of these organic molecules, then, is a balance between the favorable hydrophilic interaction and the unfavorable hydrophobic interaction. In ethanol, the hydrocarbon portion of the molecule is relatively small, and the solvation of the hydroxyl (OH) group is proportionately more significant to the solubility of the molecule. The hydroxyl group is a much less significant portion of the 1-hexanol molecule, where the hydrocarbon portion is larger, and so that compound has low water solubility as the resulting new surface that forms around the hydrocarbon portion increases the amount of less stable water molecules. The structure of 1-butanol is intermediate between those of ethanol and 1-hexanol, and so is its solubility in water.

Solvation, which is analogous to hydrogen bonding, is also important in stabilizing ions and overcomes the favorable ionic interactions within the crystal lattice. For example, when sodium chloride, NaCl, is dissolved in water, the sodium ions and the chloride ions are solvated by water molecules, so that breaking up the lattice and mixing the ions becomes favorable. On the other hand, sodium chloride does not dissolve in a hydrocarbon solvent because hydrocarbon molecules (such as hexane) cannot replace or improve upon the electrostatic interactions between the ions in the lattice (Figure 0256).

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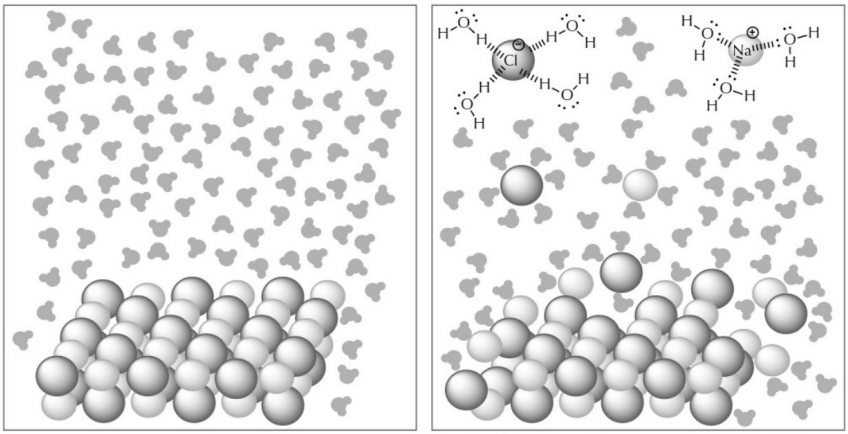
Figure 0256

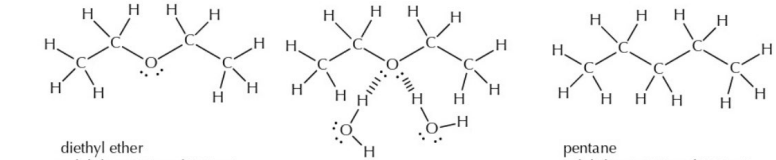
Solvation of sodium chloride in water overcomes the attraction of ions in the solid lattice, which is not possible with nonpolar solvents.


water added sodium chloride
(ionic lattice)
solvation of ions by water compensates for the lack of nearby ions, so the salt can dissolve in water

Compounds that contain oxygen or nitrogen atoms but lack hydrogen atoms bonded to these electronegative elements may participate in hydrogen bonding as hydrogen bond acceptors even though they cannot function as hydrogen bond donors. The relative solubility, in water, of diethyl ether, $CH_3CH_2OCH_2CH_3$, and pentane, $CH_3CH_2CH_2CH_2CH_3$, demonstrate this fact. Diethyl ether is almost as soluble in water as 1-butanol and much more so than pentane, which is a completely nonpolar compound containing only carbon and hydrogen atoms (Figure 0257).

Figure 0257

Solvation of organic molecules with only hydrogen bond acceptors contributes to their solubility in water.



In addition to solubility, the hydrogen bond plays an important role in chemistry and biochemistry. It is especially important in interactions between different parts of large molecules where many hydrogen bonds are possible. The shapes of enzymes, which catalyze chemical processes in the human body, can involve hydrogen bonding between distant parts of these large molecules. The two strands of the double helix of deoxyribonucleic acid (DNA) are held together by a precise pattern of hydrogen bonding believed to be responsible for the transmission of the genetic code. You will learn much more about this when we look at the structures and the chemistry of proteins, carbohydrates, and other giant molecules found in living systems.

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PRACTICE QUESTIONS

2.10 Rank the following bonds in order of anticipated bond length (1 = longest, 5 = shortest)

(a)

sp^3 C-H	
C=C	
C=O	
sp^2 N-H	
C=N	

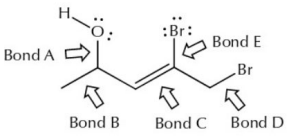
(b)

sp^2 C-H	
C≡N	
sp^2 C-O	
sp^3 S-C	
sp^3 C-O	

(c)

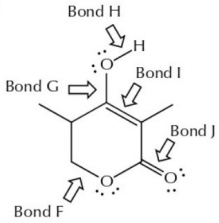
C≡C	
sp^3 C-H	
sp^3 N-H	
C≡N	
sp^2 O-H	

(d)



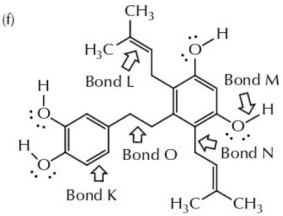
longest
shortest

(e)



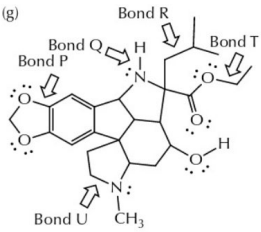
longest
shortest

(f)



longest
shortest

(g)



longest
shortest

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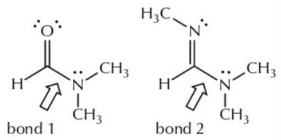
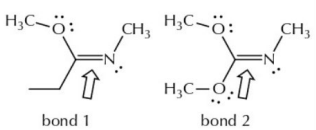
2.11 Sulfur dioxide, SO_2, has the connectivity OSO. The S-O bond length is 1.43 Å, which is shorter than the expected S-O single-bond length of 1.66 Å and the expected S=O double-bond length of 1.40 Å. The experimental O-S-O bond angle is 119.5°. Sulfur dioxide has a significant dipole moment. Write the significant resonance contributors for sulfur dioxide that are in accord with these experimental facts.

2.12 In each of the following pairs of molecules, one of the indicated carbon-nitrogen bonds is longer than the other. Tell which one is longer and provide an explanation using both words and pictures.

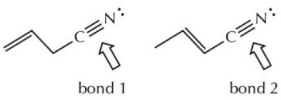
(a)



(b)



(c)



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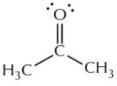
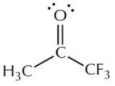
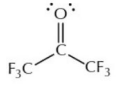
2.13 Acetone (propanone), MW 58 g/mol, has a boiling point of 56 °C, whereas 1,1,1-trifluoropropanone, MW 112 g/mol, has a boiling point of 22 °C, and 1,1,1,3,3,3-hexafluoropropanone, MW 166 g/mol, has a boiling point of -28 °C. Use words and pictures to explain the boiling point trend demonstrated by these three molecules.



acetone (propanone)
MW 58 g/mol
bp 56 °C



1,1,1-trifluoropropanone
MW 112 g/mol
bp 22 °C

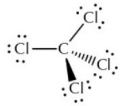


1,1,1,3,3,3-hexafluoropropanone
MW 166 g/mol
bp -28 °C

2.14 The molecular dipole moments for the first 4 hydrohalic acids (HX) are: HF (1.82 D), HCl (1.08 D), HBr (0.82 D), and HI (0.44 D). Hydrocyanic acid, HCN, has a molecular dipole moment of 2.98 D. Given that the molecular dipole moments for both dichloroacetylene (ClCCCl) and carbon tetrachloride (CCl_4) are 0 D, predict the direction and rank the relative magnitudes of the molecular dipole moments for the following set of 8 molecules.

H-F	1.82 D
H-Cl	1.08 D
H-Br	0.82 D
H-I	0.44 D
H-CN	2.98 D

dichloroacetylene
DM = 0 D

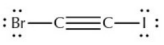


carbon tetrachloride
DM = 0 D

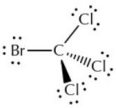
(a)

(b)

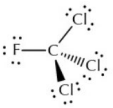
(c)



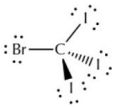
(d)



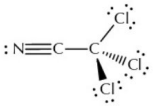
(e)



(f)

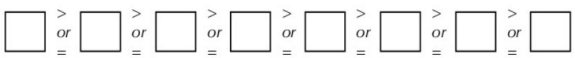


(g)



(h)

largest DM smallest DM



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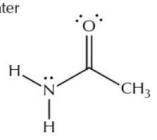
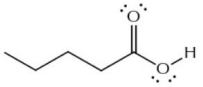
2.15 The experimentally determined water solubilities for the following organic molecules are listed below. (a) Place a circle around all of the potential hydrogen bond donor sites. (b) Place a triangle around all of the potential hydrogen bond acceptor sites. If neither exists, do not mark anything. (c) For those with a donor and/or acceptor site, draw one valid interaction with a water molecule for those that are predicted to participate in hydrogen bonding with water.

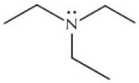
(a) acetamide
3.4 mol/100 mL water



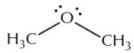
(b) pentanoic acid
0.04 mol/100 mL water



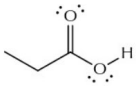
(c) triethylamine
0.05 mol/100 mL water



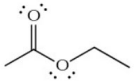
(d) dimethyl ether
7.1 mol/100 mL water



(e) propanoic acid
miscible in water

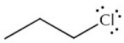


(f) ethyl acetate
0.09 mol/100 mL water

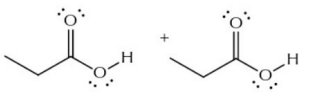


(g) triethylamine
0.81 mol/100 mL water

(h) 1-chloropropane
0.003 mol/100 mL water



2.16 Propanoic acid is observed to form a stable, hydrogen bonded dimer (two molecules of propanoic acid, together). In the structure of the dimer, each of the propanoic acid molecules is hydrogen bonded to the other with a pair of hydrogen bonds, which is an exception to the generalization about only having one hydrogen bond between any pair of partners. Draw a representation for this hydrogen bonded dimer of propanoic acid.



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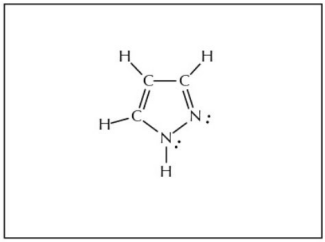
2.17 For each of the following pairs of molecules, predict and circle which one will be most soluble in water. Using words and pictures, explain your prediction.

2.18 As a general rule, atoms with nonbonding electron pairs in hybrid orbitals (localized electrons) are better hydrogen bond acceptors than atoms whose nonbonding electrons are delocalized. Given this, add two methanol (CH_3OH) molecules to the following drawing: one in which a methanol molecule serves as a hydrogen bond acceptor, and the other in which a methanol molecule serves as a hydrogen bond donor. Using words and pictures, speculate on a reason for why there should be a difference in ability between localized and delocalized electrons to be hydrogen bond acceptors.



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2.19 Using lines, dashes, and wedges to represent the direction of sigma bonds and localized nonbonding electron pairs, overlapped p orbitals for pi bonds, and individual p orbitals as needed for nbe pairs or open shell atoms, draw a three-dimensional orbital picture for the following molecules.

(a) Phosgene is a substance that is used in preparing many important organic molecules, such as the pharmaceuticals used to treat diseases. Phosgene also has had a more ominous use as a chemical warfare agent during WWI. The molecular formula and implied connectivity of phosgene is Cl_2CO.

(b) Silicon atoms, like carbon atoms, are often tetravalent. One example of this is SiF_4, silicon tetrafluoride. You do not need to show the anticipated geometry of nonbonding electron pairs on the fluorine atoms.

(c) Formaldehyde is a preservative whose distinctive odor you might recall vividly from a biology class. The molecular formula and implied connectivity of formaldehyde is H_2CO.

(d) Cyanogen is a highly toxic compound that burns with the second hottest flame during the combustion reaction between an organic molecule with oxygen. The molecular formula is C_2N_2 and the connectivity is $(CN)_2$.

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Reflections About Science: Method and Object Cannot Be Separated

Modern Western science rose at the end of the European Renaissance period, in the early 17th century. Empiricism, faithfully observing and recording phenomena, and objectivism, that there was an external truth that was knowable, defined the operations of science.

Theory had been the dominant practice, and it was used quite differently from its current meaning, where a theory is the end result of many rejected hypotheses and falsified through experiment. In the ancient sense of the term, being a theorist drew from the idea that human philosophical thought was the purest form of reasoning. If the phenomena of the world contradicted the theory, then the problem was in the experiment or the observation, not in the theory.

The ancient Greek philosopher, Plato, believed in this view of philosophy (theory), and used an allegorical story to convey his message about the purity of philosophical thought and the elevation it provides from the material world. The allegory of the cave goes like this (my paraphrasing):

> A group of prisoners has lived their entire lives chained inside of a cave, unable to move, and facing a blank wall. The wall faces away from the entrance to the cave, which sits away at some distance. A fire burns somewhere behind them and casts the shadows of people who march between them and the fire, as they carry divine icons. The combination of the cast shadows dances past the view of the chained prisoners on their blank wall. The prisoners in the cave can only describe the world they know, unknowingly looking at the shadows of shadows of the carried icons. The people chained in the cave construct a model for their reality based on what they can see.
>
> One day, a prisoner—who is the philosopher, the theorist—breaks free, escapes the cave and sees the reality of the world, as is the philosopher's curse. The philosopher returns to the cave to liberate the other prisoners with a report about the enlightened reality of the world that comes from pure thought. But the prisoners are too tied to the reality of their shadow world, and they kill the philosopher.

From my 21st century perspective, 2,400 years later, I find that Plato's allegory anticipates the shift from an objectivist (absolute fact) to nonobjectivist (relative fact) view of science that emerged in the mid-20th century. Escaping the cave of our current understanding and searching for the ultimate explanations for phenomena is a neverending quest, and each time we think we have uncovered an answer, a hundred new questions emerge. Recall Wayne Booth's definition of a critical thinker from the introductory essay in this chapter, and its conclusion: Hubris and the refusal to change keeps people chained to their old ideas and makes transformative learning impossible.

As a friend of mine, an evolutionary biologist named Craig Nelson used to say: "compared with any ultimate, knowable truth, our understanding of the world is only the next best version of 'flat earth.' The most interesting things we think we know have half-lives of 6 to12 months, and we are constantly revising our view in the light of new observations related to all of the most important things."

Every time we crawl out of one cave, we simply find we are in a new cave. Although he did not do this in the story, Plato's philosopher relinquished the chains from one cave, looking at the shadows of one reality, and traded them for another set of chains, looking at the shadows of yet another reality. Outside Plato's cave, the earth was the center of the universe and the hand of a Divine Spirit moved a great sphere on which the stars were etched.

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This strikes me as the constant dilemma and wonder of science: There can be no revealed truth because we are the ones constructing the story, and we are always limited by our experiences.

In this text, you have seen examples of this already. I was quite deliberate in Chapter 1 to say that humans invented molecules, as a solution to a problem, long before they discovered them. In this chapter, the tetrahedral atom was invented to solve a problem half a century before experimental evidence for three-dimensional shape was known. The chemical bond (as "affinity") and drawings of structures that you would recognize today (including resonance contributors) predate the discovery of electrons by 40 to 50 years. Pauling invented the idea of hybridization to reconcile conflict between the predictions from quantum mechanics and the established idea that atoms were tetrahedral. The prior ideas (what you saw inside the cave) will always influence how you interpret new perspectives when you get them.

The 17th century objectivists were convinced that science and scientific practice could stand outside of the biases of the context, experience, and the situation of the observer (to not be influenced by your prior life in the cave). A value of this perspective was that theory changed from being a perfection of abstract reasoning to something that could be argued, defended, and improved through empirical methods. A theory, as a model for the natural world, could be used to make – and test – predictions, and contradictions needed to be accommodated and, perhaps, ultimately change the theory completely.

Chemistry has been operating since about 380,000 years after the Big Bang, when the universe cooled off enough to allow electrons to be captured by protons. Fourteen billion years later, a relatively young species on our planet developed the modern study of organic chemistry, emerging in the 19th century, as we currently reckon time.

Atomic theory, revived in the 1700s, meant that elements were soon to be known, and analytical measurements could be made to identify them. Justus von Liebig, in early 19th century Germany, gets a lot of historical credit for helping to establish the laboratory practices of organic chemistry, including recording reports in a public format (journals) and establishing a teaching laboratory for teaching and training in an academic setting, which had never been done before. Yet even Liebig, who is seen as a premiere experimentalist, was still the product of his own education (his own cave). His written correspondence with the Swedish chemist Berzelius has been preserved, and in an 1834 letter from Liebig to Berzelius, he opines about the modern, experimental science of chemistry:

> "Die schönsten Theorien werden durch die verdammten Ver¬suche über den Haufen geworfen, es ist gar keine Freude mehr Chemiker zu sein."
>
> "The most beautiful theories are thrown onto the heap by these damned experiments, it is no fun at all to be a chemist any more."
>
> J. J. Berzelius, *Berzelius und Liebig—Ihre Briefe von 1831–1845*, **1982**, 94.

In the early 20th century, relativity and quantum mechanics forced us to face the fact that we were all still chained inside the cave of the macroscopic world we inhabit. When you do an experiment on electrons to look for the wave properties you are familiar with… you see those properties. And when you do an experiment on electrons to look for the particle properties you are familiar with, you see those, too. The experiment you do affects what you see, and for the first time in history, there was a widespread realization that scientific truth was not an absolute observable, disconnected from the decisions made by the observer.

Werner Heisenberg, who made pioneering contributions to the development of quantum mechanics, also understood the philosophical limitations to objectivism, that we are bound by the chains of our particular cave, or worldview and experience, in trying to describe the shadows we see. In 1958, reflecting

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on 30 years of contributions to science, he spends time expressing the same sort of frustration that Liebig had done, over a century earlier:

> "Modern man confronts only himself… The scientific method of analyzing, explaining and classifying has become conscious of its limitations, which arise out of the fact that by its intervention science alters and refashions the object of investigation. In other words, method and object can no longer be separated. The scientific world-view has ceased to be a scientific view in the true sense of the word."
>
> W Heisenberg (Pomerans translation), *The Physicist's Conception of Nature*, **1958**, 29.

This realization is quite profound: "Method (how we observe and think about observing) and object (what we describe) can no longer be separated."

Standing outside of the cave, in other words, is not standing outside of reality.

In this chapter, there are many depictions of bonding. In the discussion about delocalization, I emphasized this key fact: We do not use resonance contributors because they are good or better at representing the objective reality of molecular structure, we use them because it is convenient, and because a more complicated system of drawing would likely make communication worse, not better. We assume that bonds are a shared electron pair, yet if electrons are better off when they are delocalized over more than two nuclei, then why aren't all the electrons in a molecule delocalized over all of the atoms? Spoiler alert: They are.

The drawings we use, with lines, dashes, and wedges, or those with p orbitals, or a pair of dots for a nonbonding electron pair, are placeholders for whatever the underlying reality of molecules might be. Arguments about "right" and wrong" or "better" and "worse" are irrelevant, relative to the question "is the model you are using operationally useful… does it do the things you need it to do?" Two hundred years ago, chemists concluded that there was something that must be holding atoms in place and called it chemical affinity. The term affinity evolved to become chemical bond, and we have expanded what "chemical bond" means for over a hundred years. In a 2011 commentary in *Nature*, titled "Beyond the Bond," Philip Ball used the subtitle "More than ever before, new techniques show the bond to be a convenient fiction, albeit one that holds the field of chemistry together."

Ball quotes two chemistry luminaries, Linus Pauling and Roald Hoffmann, regarding the idea of the chemical bond:

> There is, for example, the matter of when to regard two atoms as being bonded at all. Pauling's somewhat tautological definition rather gave the game away: a group of atoms is to be considered bonded when it is "convenient for the chemist to consider it as an independent molecular species."
>
> As Hoffmann says: "Any rigorous definition of a chemical bond is bound to be impoverishing." His advice to "have fun with the fuzzy richness of the idea" is well worth heeding.
>
> P Ball, "Beyond the Bond" *Nature*, **2011**, *469*, 26.

And if the chemical bond is not a settled issue, then every story we tell using bonds needs to be seen as tentative as the shadow on the wall of a cave.

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Summary

The structure of organic molecules can be understood as the connectivity of the atoms and their arrangement in space. Although, in our drawing system, we use integer representations for bond order (single, double, triple) and formal charges (-1, 0, +1), experimental observations of reactivity, and then of bond distances, actual molecules are built with a full and continuous spectrum of bonding.

Electron delocalization is the model used to account for the effects on structure and reactivity due to a full spectrum of bonding, using the standard bond orders and charges, and thinking of molecules comprising partial, or intermediate, bonds and charges. Electrons can be classified as localized (the framework that maintains the connectivity) and delocalized (their distribution over multiple atoms, which is a stabilizing and therefore favorable effect). The collection of drawings that maintains the positions of the atoms and the localized electrons but shows the possible redistribution arrangements of the delocalizable electrons, are called the resonance contributors to the actual structure. The actual structure needs to be imagined as the weighted average (contribution) of these forms, according to their relative importance according to the standard rules of stability for molecular structures (closed shell atoms, uncharged atoms, placement of charges, and proximity of charges).

Classifying a molecular structural drawing according to its anticipated localized and delocalizable electrons is a core skill in organic chemistry, as vital to understanding how to communicate about structure and reactions as how the line drawing itself represents atoms. Typically, only one resonance contributor is drawn in the course of normal communication about a structure, and it must be read not only as a collection but also as an imprecise representation, based on how each member of the collection might contribute to the actual structure.

Fortunately, the guidelines that cover which electrons are delocalizable are easily and consistently applied to all molecules and involve identifying multiple bonds and their structural relationship with each other, with atoms bearing nbe pairs, and with open shell atoms. When they are drawn out, resonance contributors are visually linked together with the uniquely used double-headed arrow in between the drawings.

Because electron delocalization fundamentally affects structure, all other models for bonding need to account for the effects attributed to delocalization. Creating 3D drawings for molecules that also account for orbital contributions is an excellent example of how significant a role delocalization plays in directing bonding models to account for it.

Starting with the standard drawing of a single resonance contributor, its membership among a collection of drawing needs to be assessed by identifying whether it has any delocalizable electrons. Models of molecular geometry are ultimately atom-centered because we cannot experimentally locate electrons. The VSEPR model for geometry is centered at the atom center and based on how the localized electron pairs will be distributed around the atom. The VSEPR model, for organic main group elements, only needs to account for 4, 3, or 2 localized electron pairs, and describe electronic geometries of tetrahedral, trigonal planar, or linear, respectively. Observable geometries are based on the atoms surrounding the original atom center because electrons are not observable.

The sp^3 hybridization model was developed to reconcile the observations of nonequivalent valence electrons (as specified by the orbital picture of atoms) and the long-standing belief that individual chemical bonds were equivalent. Other hybridizations (sp^2 and sp) rapidly developed to account for delocalizable electrons. In the end, the hybridization and VSEPR models intersect in describing the localized electrons being sigma (σ) bonds or nbe pairs occupying hybrid orbitals (VSEPR 4 = sp^3; VSEPR 3 = sp^2; VSEPR 2 = sp) and the delocalizable electrons occupying the unhybridized p orbitals, either as pi (π) bonds or nbe pairs. Or, in the case of open shell atoms, the p orbital can be unoccupied.

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The experimental X-ray crystallography technique provided the first direct evidence for the location of atoms in space, within a molecule, and so revealed the different bond lengths that exist in actual structures. Besides providing support for the delocalization model, because of the observed spectrum of bond lengths, the number of observations led to useful generalizations about what factors affect bond length (differences in intrinsic atom size according to the period, differences in bond order, differences in electronegativity, and partial bond character because of delocalization).

The fundamental electrostatic force that underlies bonding (charge/charge attraction of protons for electrons) is also responsible for the variety of intermolecular interactions that affect properties such as boiling point. Van der Waals interactions are individually weak but cumulatively strong because they increase with the number of protons and electrons in one molecule that become attraction to those in another, either intrinsically (London dispersion forces) or when collisions induce temporary dipoles to form. Molecules with molecular dipole moments experience the relatively stronger dipole-dipole attraction, which is also a van der Waals interaction. In hydrogen bonding, highly polarized covalent bonds involving hydrogen atoms (hydrogen bond donor) can attract an electron pair from another atom (hydrogen bond acceptor) to share electron density with the electron-poor hydrogen atom. Hydrogen bonding can have a strong effect on molecular properties such as boiling point and solubility of organic molecules in water.

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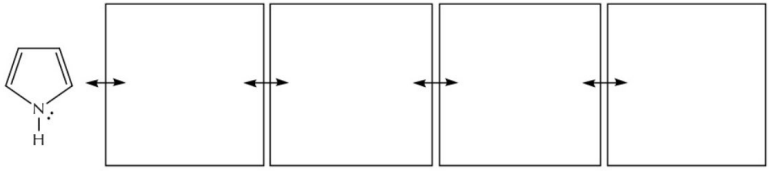
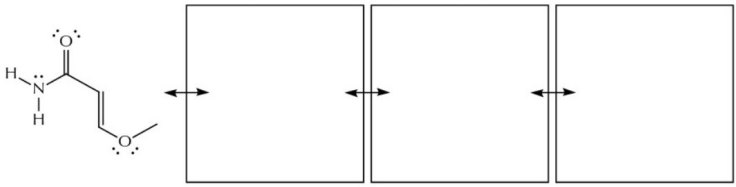
CHAPTER QUESTIONS

2.20 Each of the following molecules has the specified number of additional resonance contributors that have all closed shell atoms and maintain formal charges in the [-1, +1] range. Draw them, including nbe and charges.

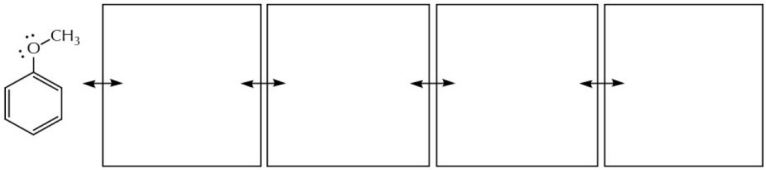
(a) 4 additional resonance contributors



(b) 3 additional resonance contributors (none with over 2 formal charges per structure)

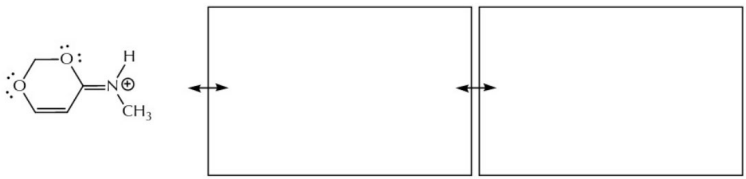


(c) 4 additional resonance contributors



(d) 2 additional resonance contributors

(e) 2 additional resonance contributors (restricted to 1 formal charge per structure)



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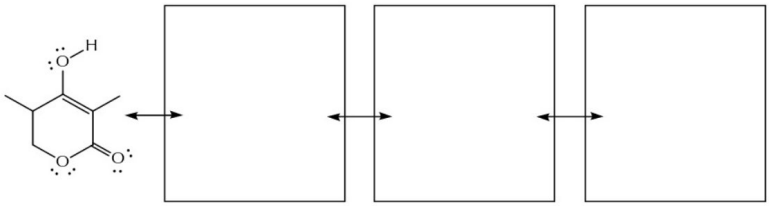
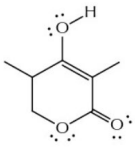
2.21 The lankacidins were discovered in the extracts of *Streptomyces rochei* over fifty years ago and they show strong antibiotic activity against Gram-positive bacteria (*Angew Chem Int Ed* **2018**, *41*, 13551). The lankacidin structure includes the structural subunit, shown below.

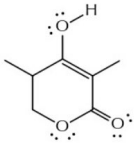
(a) This compound has three other resonance contributors with all closed shell atoms, formal charges between [-1, +1], and a maximum of two atoms with formal charges. Draw these three resonance contributors.



(b) Based on an analysis of the set of resonance contributors, one of the atoms in this compound is predicted to be a significantly better hydrogen bond acceptor than the other atoms. Using methanol (H–Ö-CH_3) as hydrogen bond donor, show the best hydrogen bond (using the dashed line notation, ||||||||) between this compound and one molecule of methanol. What is the explanation for your selection?



(c) Using lines, dashes, and wedges for localized electrons and unhybridized p orbitals for delocalizable electrons, draw the 3D orbital picture for this resonance contributor of this molecule.



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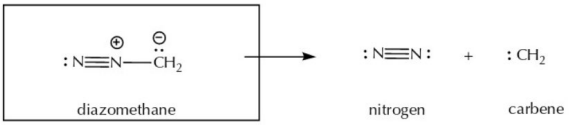
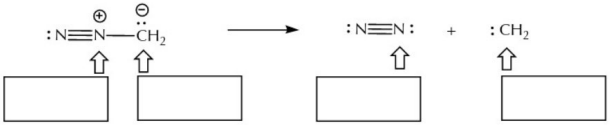
2.22 Carbenes are a classification of reactive intermediates that have been studied for many years (*JACS* **1959**, *81*, 5874). In this old study, the simplest carbene (molecular formula "$:CH_2$" possessing an open shell, sextet carbon) was studied. The reaction is shown below.

(a) Provide the curved arrow mechanism for the formation of carbene from its diazomethane starting material.



(b) Assign the hybridization to each of the atoms indicated here:



(c) Draw the 3D orbital representation for carbene. Use lines, dashes, and wedges for localized electron pairs (sigma bonds and localized nonbonding electron pairs) and p orbitals that are either empty, full, or being used for pi bonds.

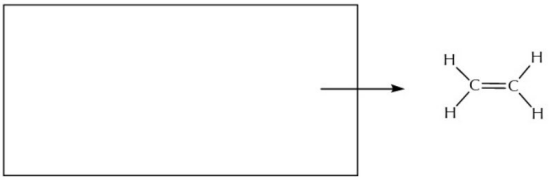
$:CH_2$

carbene

(d) When carbene forms, one thing it can do is react with itself to give an all closed shell atom product, according to the equation [$:CH_2 + :CH_2 \rightarrow H_2C{=}CH_2$]. Using standard, non-3D Lewis structures (lines for bonds, plus nonbonding electron pairs), draw out this complete reaction, which takes place in one mechanistic step, using the curved arrow notation. Provide the drawings for two things:

(i) the two $:CH_2$ (carbene) reactants

(ii) the curved arrow notation for the one-step mechanism



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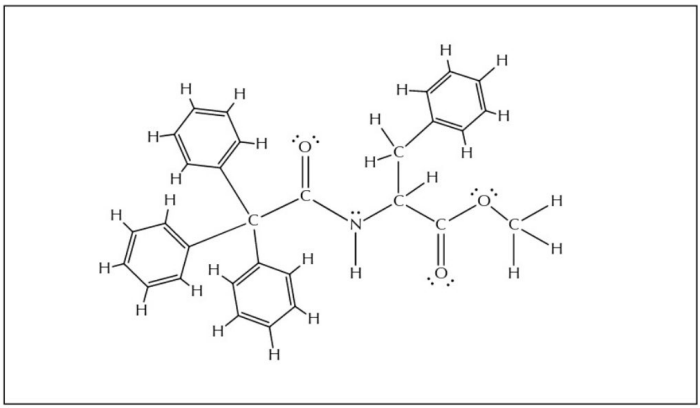
2.23 Triphenylmethylamides are a new class of pharmaceutical that has proven effective in causing cell death in melanoma (skin cancer) cells. The triphenylmethylamide shown below has a single best hydrogen bond donor site, and a single best hydrogen bond acceptor site. Add two water molecules to this drawing and show them with an appropriate hydrogen bonding interaction (use a dashed line) with these two sites.

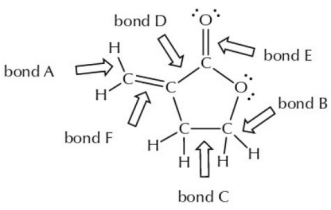


2.24 Draw the Lewis structure for a C_6O_6 isomer with the following properties:

(a) all closed shell atoms
(b) all atoms uncharged
(c) no molecular dipole moment

There are multiple correct answers that meet these criteria, so this is a great question for sharing answers with others.

2.25 α-Methylene-γ-butyrolactone is one of the compounds that gives the red American rose its distinctive odor. Rank the 6 bonds (A-F) in the anticipated order of bond length.



longest bond

shortest bond

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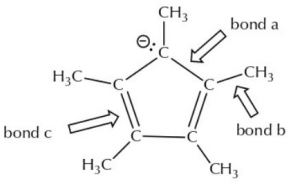
2.26 The following anion has been studied extensively. It has a number of all closed shell atom resonance forms. Considering the collection of resonance contributors and their relative significance, answer the questions about the actual molecular structure of the anion (i.e., based on its collection of resonance contributors).



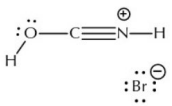
(a) circle one Bond a is [longer than / equal to / shorter than] bond b.

(b) circle one Bond a is [longer than / equal to / shorter than] bond c.

(c) circle one Bond b is [longer than / equal to / shorter than] bond c.

(d) According to its collection of significant resonance contributors, the negative charge can be delocalized to how many of the carbon atoms in this anion?

2.27 Draw a three-dimensional orbital representation for both ions of the compound shown below. Use lines, dashes, and wedges where necessary for sigma bonds and the direction of nonbonding electron pairs, p orbitals for lone p orbitals and overlapped p orbitals for pi bonds.



2.28 Methanol (connectivity CH_3OH) is both a hydrogen bond donor and an acceptor. Draw out four (4) methanol molecules and show how they might be hydrogen bonded to each other as a cluster of four molecules (as opposed to, say, 2 groups of 2). There are many correct answers (and many incorrect ones). Include nonbonding electron pairs in your drawings, and show hydrogen bonds as dashed lines.

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2.29 Based on an empirical molecular formula of $C_6H_8O_2$, draw a molecular structure that meets these criteria:

(i) all closed shell atoms
(ii) no formal charges on any of the atoms
(iii) no molecular dipole moment

2.30 Cyanogen bromide (connectivity BrCN) is a toxic compound used to control pests.

(a) How many units of unsaturation does cyanogen bromide have?

(b) (i) Draw the complete Lewis structure for cyanogen bromide.
(ii) Assign the hybridizations to the atoms.

(c) Using lines, dashes, and wedges for sigma bonds and to designate the direction of non-bonding electron pairs, and overlapping p orbitals for pi bonds, provide a three-dimensional drawing for the BrCN molecule.

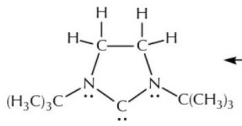
(d) Given: the following molecular dipole moments:

$CH_3CN = 3.88$ Debye
$CH_3C{\equiv}C{-}Br = 1.33$ Debye

Predict and show the direction of the molecular dipole moment for BrCN (2.99 Debye).

BrCN

2.31 Carbenes are a class of organic molecules with an uncharged carbon atom carrying an open shell sextet electron configuration. The preparation and properties of the following carbene was reported (*J Org Chem* **2003**, *68*, 2812). Draw the two all closed shell atom resonance structures for this molecule.



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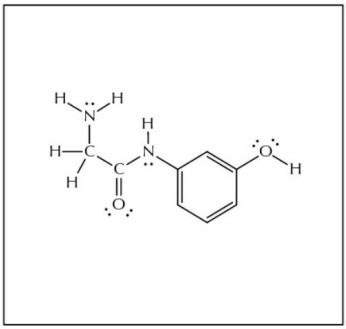
2.32 With respect to the molecule shown here:

(a) Draw a water molecule that is hydrogen bonded to the best anticipated hydrogen bond acceptor.

(b) Draw a water molecule that is hydrogen bonded to the best anticipated hydrogen bond donor.

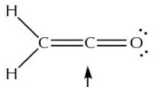
(c) Put a circle around the pair of atoms that have the shortest bond length.



2.33 Ketene is one of the C_2H_2O isomers. Its Lewis structure is shown here.

(a) This drawing (contributor A) is one of a pair of resonance contributors that represent the actual structure of ketene. Draw the other resonance contributor (B) for ketene that maintains all closed shell atoms.

ketene resonance contributor A



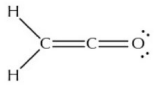
ketene resonance contributor B

(b) Is the resonance form of ketene that was drawn on the page already a more significant, less significant, or equivalent contributor to the actual structure of this molecule compared with the one you drew in part (a)? Why?

the original resonance form is of: more less equivalent significance compared with (a).	briefly state why

(c) Using lines, dashes, and wedges for sigma bonds, as well as for indicating the directionality of nonbonding electron pairs, and using overlapped p orbitals for pi bonds as well as for filled or empty lone p orbitals as necessary, provide a three-dimensional orbital drawing for the resonance contributor A.

ketene resonance contributor A



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2.34 There are several structural (constitutional) isomers with the molecular formula C_3H_7NO. Draw the structures for two of these isomers that meet the criteria listed below. All atoms should be closed shell with no formal charges, and nonbonding electron pairs should be shown.

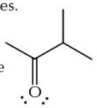
(a) Contains a 4-atom ring and a hydroxyl group

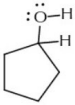
(b) Contains a nitrogen-oxygen double bond

2.35 Sulfur dioxide (SO_2) has a molecular dipole moment of 1.60 D, whereas carbon dioxide (CO_2) has a molecular dipole of 0.00 D, in spite of the fact that CO bonds are more polar than SO bonds. Use structures and words to provide a brief explanation for this difference between SO_2 and CO_2.

2.36 The following three $C_5H_{10}O$ isomers have signficantly different solubilities in water at 20 °C. Match each one with its solubility and provide an explanation for the differences.

tetrahydropyran

isopropyl methyl ketone 

cyclopentanol 

circle one:		
7 g/L	38 g/L	79 g/L

circle one:		
7 g/L	38 g/L	79 g/L

circle one:		
7 g/L	38 g/L	79 g/L

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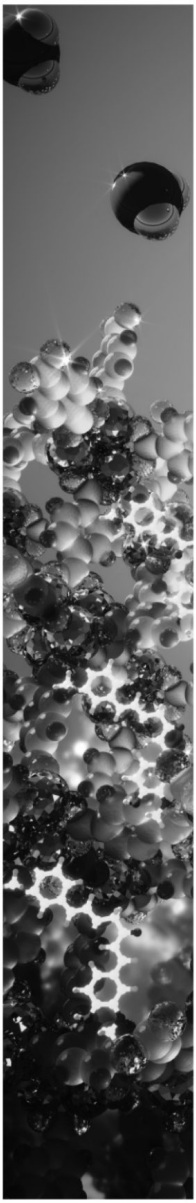

CHAPTER 3

Reactions of Organic Compounds as Acids and Bases

Setting the Stage: The Power of Analogies in Creating Models

3.1 Lewis Acid-Base Reactions

A. Reactivity of Open Shell Atoms
B. Curved Arrow Convention and the Organic Reaction Mechanism
C. Complexation-Decomplexation Reactions of Lewis Acids and Bases
D. Evaluating the Position of the Lewis Acid-Base Equilibrium

PRACTICE QUESTIONS

3.2 Brønsted Acid-Base Reactions

A. Reactivity of Brønsted Acids and Bases
B. Curved Arrow Convention and the Organic Reaction Mechanism
C. Are There Free Protons in a Reaction Flask? The Lewis Versus Brønsted Acid Debate
D. Evaluating the Position of the Brønsted Acid-Base Equilibrium

PRACTICE QUESTIONS

3.3 The Quantitative Scale for Brønsted Acidity

A. Which Acid Is Stronger?
B. A Quantitative pK_a Scale Based on Dissociation of Acids in Water
C. Reading Equations in Chemistry and Mathematics
D. Structural Trends and Brønsted Acidity

PRACTICE QUESTIONS

3.4 Evaluating Brønsted Acid-Base Reactions

A. Predicting the Brønsted Acidity (pK_a Values) for Unfamiliar Compounds
B. Using pK_a Values for Assessing Base Strength
C. Predicting and Evaluating Brønsted Acid-Base Reactions (and Revisiting Hydrogen Bonding)
D. The Relationship Between pH and the Composition of a Solution

PRACTICE QUESTIONS

Reflections About Science: Relative Measurement and Points of Reference

Summary

CHAPTER QUESTIONS

EXAM QUESTIONS (CHAPTERS 1–3)

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CHAPTER 3

Reactions of Organic Compounds as Acids and Bases

Setting the Stage: The Power of Analogies in Creating Models

When you need to explain something that is completely outside the experience of your audience, analogies can provide a useful way to communicate your understanding. Analogies start with familiar, prior knowledge and then make the claim that what you understand about that familiar system can be applied to a new one.

Analogies are a part of everyday language. How hard was it to find your friend at a large concert venue after the battery in your phone ran out of power? *It was like finding a needle in a haystack.* Mathematician, philosopher, and scientist René Descartes, who championed body-mind duality, developed the analogy of the *body as a machine* in his 1633 publication, *Traité de l'Homme.*

There are a few quite familiar examples of analogies in chemistry. In 1915, Niels Bohr used the idea of the planets in our solar system orbiting the sun to build his model for how the negatively charged electrons surround the positively charged nucleus at specific distances. The differences in orbit size were assigned as energy levels to explain the line spectra observed for the emission of light as electrons make transitions from one orbit to another (Figure 0301).

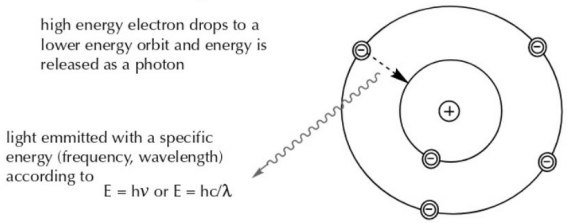
high energy electron drops to a lower energy orbit and energy is released as a photon
light emmitted with a specific energy (frequency, wavelength) according to
E = hν or E = hc/λ

Figure 0301
The Bohr planetary model for atomic structure.

In the 1930s, chemists including Michael Polanyi used the analogy of the collision of billiard balls (Figure 0302) to describe the behavior of collections of atoms interacting with one another, including the need for specific trajectories for productive reactions to occur (while a poor trajectory only results in atoms and molecules bouncing off each other).

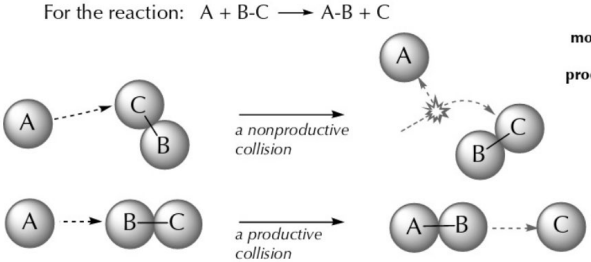

Figure 0302
The billiard ball model for molecular collisions and productive reactions.

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Even the simple choice to use a familiar word for a new and unfamiliar process is an example of a useful analogy. In the mid-1800s, reactions were observed in which all of the constituent atoms of the starting materials were combined into a single product (e.g., $C_5H_{10} + Br_2 \rightarrow C_5H_{10}Br_2$). Particularly in an era where only the molecular formula could be determined, the observed outcome could have been called many different things: a "combination reaction," an "amalgamation reaction," a "merger reaction," a "consolidation reaction," or even an invented term such as *reactionis coniunctio* ("a joining reaction"). None of these were used, but the historical adoption of the term "addition reaction" was, arguably, an excellent choice because the molecular formulas are adding their atoms together as one might find in the familiar addition process of mathematics.

With over 12 million known organic molecules having been identified over the last 200–250 years, analogies play a key role in how we understand or make predictions about the structure and reactivity of new and unfamiliar molecules. One of the exciting revelations from studying organic chemistry is how, after only a year, you can understand significant aspects of state-of-the-art research in the field of organic chemistry as well as parts of applied areas such as materials science, drug discovery, environmental science, medicinal chemistry, and other biomedical life sciences. This chapter introduces acid-base reactivity, which is a powerful source of analogies for organic chemical reactions.

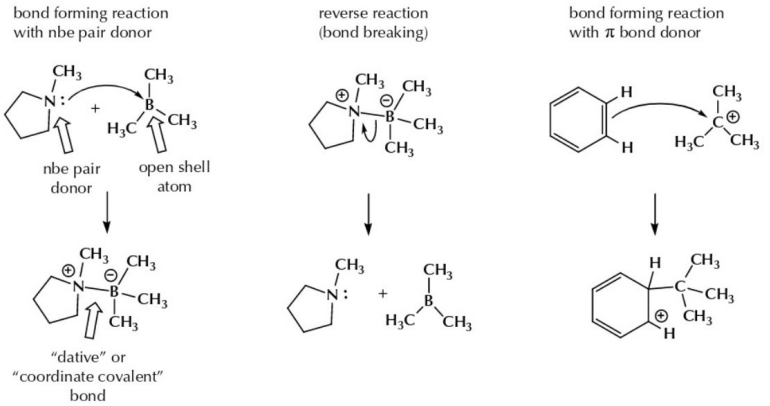
3.1 Lewis Acid-Base Reactions

A. Reactivity of Open Shell Atoms

In Section 1.4B (Open Shell Atoms and Their Reactivity), the reactivity of open shell atoms was introduced. The drive to achieve closed shell electron configurations explains a great deal of bonding in the organic main group elements (duet rule for hydrogen atoms; octet rule for carbon through fluorine atoms). Open shell atoms routinely combine with other atoms that have sharable electron pairs to make new covalent bonds where both of the electrons have come from a nbe pair or a π bond. This type of covalent bond, where both of the electrons have come from the same source, has been historically known as a "dative bond" or a "coordinate covalent bond" (Figure 0303).

Figure 0303

Reactivity of open shell organic main group elements.


bond forming reaction with nbe pair donor
reverse reaction (bond breaking)
bond forming reaction with π bond donor
nbe pair donor
open shell atom
"dative" or "coordinate covalent" bond

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B. Curved Arrow Convention and the Organic Reaction Mechanism

The reaction of open shell atoms with electron pair donors is one of the simplest reactions to depict using the curved arrow notation. This notation was introduced in Section 1.4D (Using the Curved Arrow Notation to Represent Bonding Changes) using the reactivity of open shell atoms and atoms with nbe as electron donors (Figures 0153 and 0154). You should review or refresh your understanding of the curved arrow notation, if needed. A few representative examples of the open shell atom mechanism and the curved arrow notation are provided in Figure 0303, including the forward reaction (bond formation with a nbe pair donor), the reverse reaction (bond breaking to release a nbe pair), and a reaction where a π bond serves as an electron pair donor.

C. Complexation-Decomplexation Reactions of Lewis Acids and Bases

As chemists began to generally accept the idea that chemical bonding was due to shared electrons, the models for understanding reactivity moved from atom-centered (where the atoms were the core, defining actors) to electron-centered explanations. In the early 1920s, Gilbert N. Lewis recommended using an electron pair donor-acceptor model to define reactivity. This model came to be known as Lewis acid-base chemistry.

An open shell atom can accept an electron pair, and that molecule is called a Lewis acid. In the main group organic elements, this means that Lewis acids will react to go from open shell to closed shell electron configurations (as in Figure 0303). The electron pair donor that provides the electrons to the Lewis acid, used to form a new covalent bond, is called the Lewis base.

Forming a dative, or coordinate covalent bond, where both of the electrons in the bond come from the same atom, is commonly called a complexation reaction. The bonds that are formed in this way are generally formed reversibly, which means that they can sometimes break as readily as they form, restoring the electron pair to its original atom as well as reforming the open shell atom. The reverse reaction for a complexation can be called a decomplexation reaction or a dissociation reaction.

It is important to remember that Lewis did not grow up knowing about electrons. To him, chemical affinity ("bonding") was an ionic force with no model for its origins, and he would have imagined that HCl was [H^+ Cl^-], or that sometimes atoms cluster in groups, so that H_2O was [H^+ OH^-] or chloromethane, CH_3Cl, was [CH_3^+ Cl^-]. With the discovery and application of electrons to chemical bonding, all bonds, to Lewis, were the combination of an open shell electron pair acceptor with an electron pair donor, resulting in a closed shell ("stable group") structure:

> It seems to me that with complete generality we may say that a basic substance is one which has a lone pair of electrons which may be used to complete the stable group of another atom and that an acid substance is one which can employ a lone pair from another molecule in completing the stable group of one of its own atoms. In other words, the basic substance furnishes a pair of electrons for a chemical bond; the acid substance accepts such a pair.
>
> GN Lewis, *Valence and the Structure of Atoms and Molecules*, New York: The Chemical Catalog Co., **1923**, 141.

Figure 0304 shows a set of complexation/decomplexation (Lewis acid-base) reactions. The Lewis acids and bases are labeled, as are the complexes. In organic compounds, the most commonly encountered Lewis acids contain open shell atoms from the boron group (boron, aluminum, gallium) or cationic carbon atoms (carbocations). A boron and a gallium example are included in the figure.

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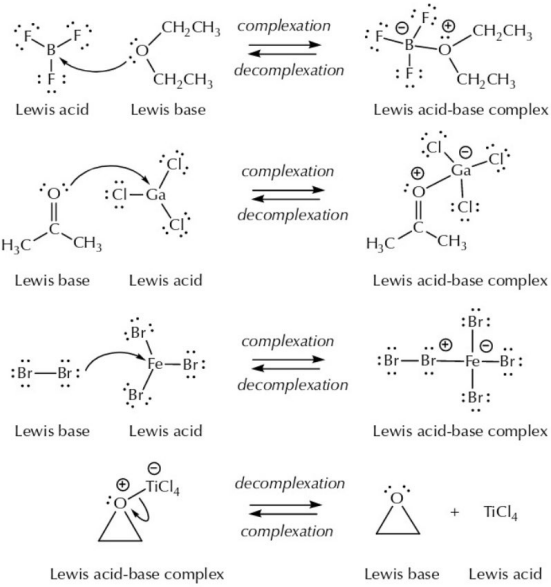
Figure 0304
Lewis acid-base (complexation-decomplexation) reactions.



As is also shown in Figure 0304, various transition metal atoms and their ions act as Lewis acids, and they are often used for catalyzing organic chemical reactions. The Lewis acids that are useful in these reactions are determined empirically, that is, through experiment. While there are many Lewis acid candidates, the ones that are going to work well in an actual chemical reaction are difficult to predict or make too many generalizations about. These Lewis acids will be introduced, gradually, as they are needed. Some examples of useful Lewis acids that include transition metal ions are titanium tetrachloride ($TiCl_4$, in the figure), ferric bromide ($FeBr_3$, in the figure), zinc chloride ($ZnCl_2$), tin tetrachloride ($SnCl_4$), and silver nitrate ($AgNO_3$). Although it is difficult to predict exactly which Lewis acid will be the best complexing agent in a reaction, if you have the experimental evidence that it does work (i.e., you are told), then you can apply the general idea of Lewis acid-base chemistry and predict the structure of the complex and show a curved arrow mechanism for its formation.

In the examples shown in Figure 0304, the complexation (bond forming) and decomplexation (bond breaking) labels are associated with the direction of each arrow. There is no inference that the right- or left-hand side of these equations is more or less stable, based upon the way the equations are drawn. Evaluating the position of the equilibrium is a separate consideration, taken up in the next section, and cannot be assumed by the decision on how the drawing is laid out.

D. Evaluating the Position of the Lewis Acid-Base Equilibrium

When there is only one possible complex that can form, the position of the equilibrium can be reliably predicted, because the complexation reactions of main group, open shell atoms form closed shell products. With the generalization that closed shell atoms are more stable than open shell atoms, the equilibria for these complexation/decomplexation reactions favor the side with the formed complex.

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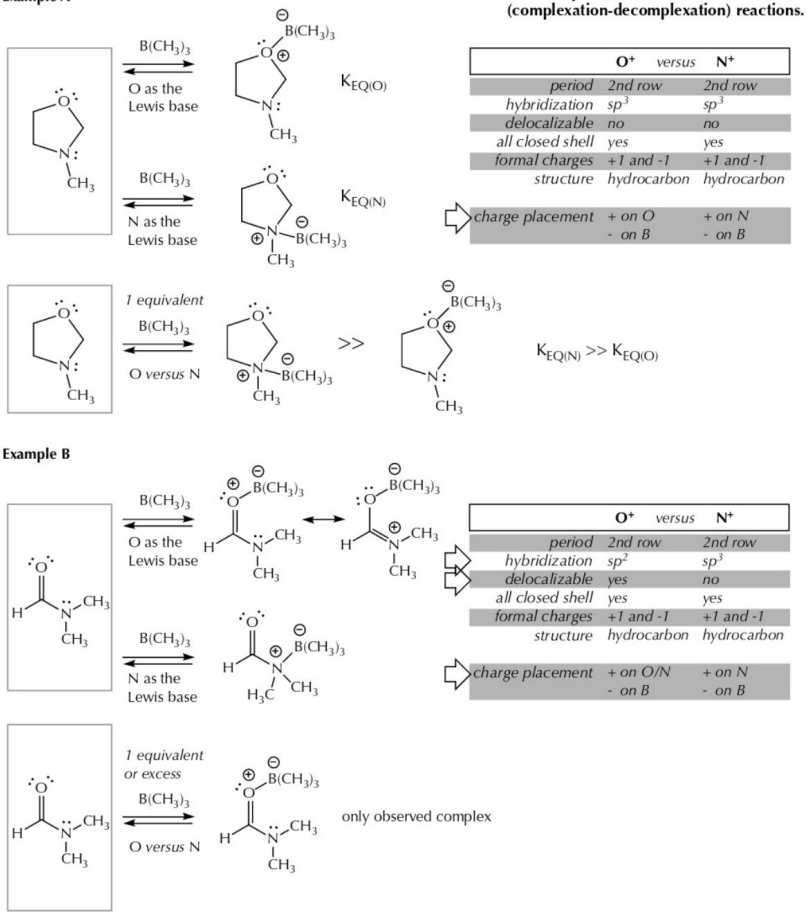
In Figure 0304, as written, the first three entries would be expected to have $K_{EQ} > 1$ (as written, complex on the right-hand side) and $K_{EQ} < 1$ for the fourth entry (complex on the left-hand side).

Many molecules have more than one possible Lewis basic site, and so forming different complexes is possible, and there is an implicit competition between multiple equilibria that needs to be resolved. In some cases, the standard guidelines for evaluating the stability of organic structures can be used to make the decision about which one is more favorable, that is, which one has the higher equilibrium constant. Figure 0305 shows two examples of such a competition, where the molecule with both a nitrogen and oxygen atom as Lewis base candidates could each form a complex.

Figure 0305

Competition between Lewis acid-base (complexation-decomplexation) reactions.



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Example A. Comparing the two complexes, nitrogen atom versus oxygen atom acting as the Lewis base, the N and O atoms (a) are in the second row, (b) are sp^3, (c) have no opportunity to delocalize the charge, (d) are in a molecule with all closed shell atoms, (e) possess the same formal charge (+1), and (f) occupy the molecule in similar structural environments. These are the same criteria you used when assessing resonance contributors because they are the standard criteria for assessing the stability of organic molecules. As was true when making assessments about resonance contributors, charge placement is a favor that needs to be considered, and this is the most significant difference between these two complexes. A positive charge is more stable on the less electronegative nitrogen atom than on the more electronegative oxygen atom.

Although the actual quantitative values for the equilibrium constants would require experimental results, it can be anticipated that the K_{EQ} for the complexation with the nitrogen atom is larger than that for the oxygen atom. This predicted difference in the K_{EQ} values means that a 1:1 mixture of the molecule with the Lewis basic sites and the Lewis acid would be expected to show selectivity in favor of the complexation reaction with the nitrogen atom.

Example B. The second example is another nitrogen versus oxygen atom competition, but the comparison is more complex. The nbe pairs on the oxygen atom are localized, while the pair at the nitrogen is delocalizable. Looking at the two possible complexes, there are three differences to consider. First, in Example A, the charge placement was cleanly on the nitrogen atom versus the oxygen atom, favoring the complexation with the nitrogen atom. In Example B, however, the positive charge derived from complexation with the oxygen atom is shared between the oxygen atoms and the nitrogen atom. Second, the complexation of the boron atom changes the hybridization of the nitrogen atom from sp^2 to sp^3, which is a less electronegative hybridization, and would favor the complexation with the nitrogen atom. Finally, as implied above, the positive charge on the oxygen is delocalized, thanks to the nitrogen atom, while the positive charge on the nitrogen atom is localized. The three criteria do not all point to the same conclusion.

In Example B, you need the experimental result to resolve the dilemma, because there is no absolute ranking of these various criteria. On the other hand, built upon your prior experience with evaluating resonance contributors, you may already be developing a chemical intuition that is telling you that the stability associated with delocalization may be more significant than charge placement and hybridization. In fact, experimentally, there is only evidence for the complexation at the oxygen atom, which is consistent with the importance that electron delocalization plays in contributing to molecular stability.

These two examples are important to contemplate, because they are a reminder, as was true in evaluating resonance contributors, that it will not always be possible to use a single principle, such as the electronegativity difference between the nitrogen and oxygen atoms, to make predictions about relative reactivity. When different structural factors are involved (closed shell, charge, charge placement, hybridization, delocalization), there is no absolute ranking for their effects, and so experimental observations are needed to explain the results.

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D. Evaluating the Position of ...
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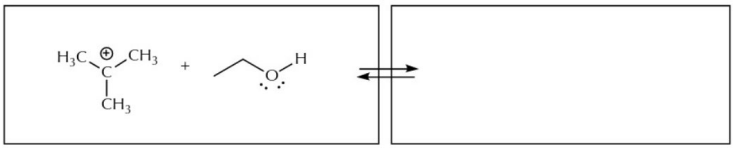
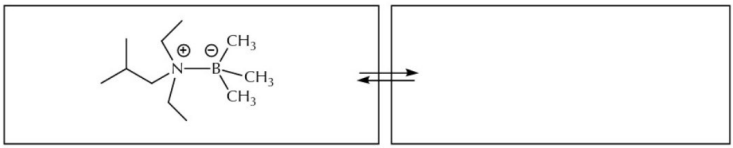
PRACTICE QUESTIONS

3.01 Based upon Lewis acid-base chemistry, the following examples either show complexation, in which case you should draw the complex, or decomplexation, in which case you should draw the separated Lewis acid-base pair. Include the curved arrow notation for the mechanisms.

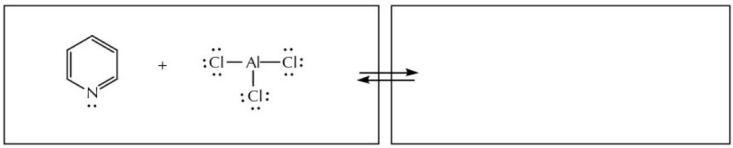
(a)



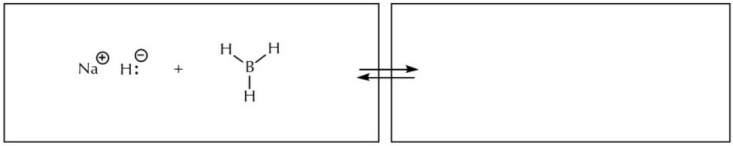
(b)



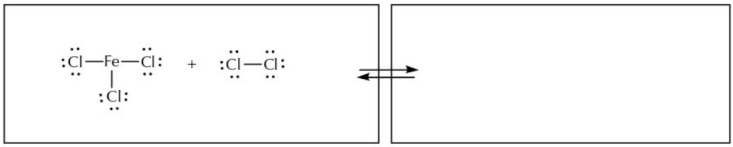
(c)



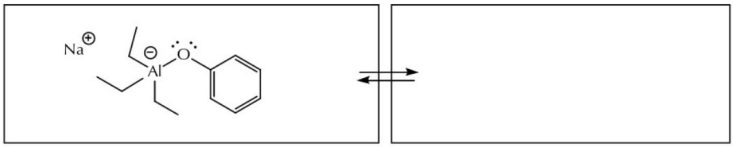
(d)



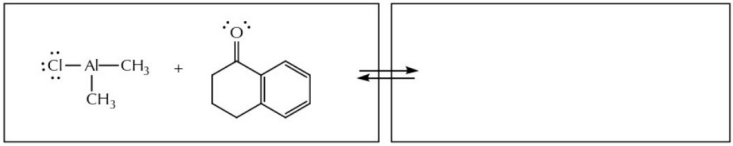
(e)



(f)



(g)



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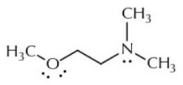
3.02 Boron trifluoride (BF_3) is a commonly used Lewis acid in organic chemistry. Each of the following molecules has two potentially Lewis basic atoms. Provide structures for the more and less favorable (stable) Lewis acid-base complexes anticipated for each of the following molecules, and briefly indicate the reason for the choice.

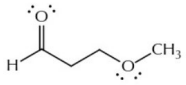
(a)



more favorable BF_3 complex	less favorable BF_3 complex

explanation:

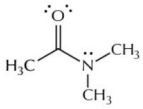
(b)



more favorable BF_3 complex	less favorable BF_3 complex

explanation:

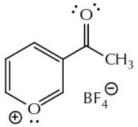
(c)



more favorable BF_3 complex	less favorable BF_3 complex

explanation:

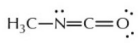
(d)



more favorable BF_3 complex	less favorable BF_3 complex

explanation:

(e)



more favorable BF_3 complex	less favorable BF_3 complex

explanation:

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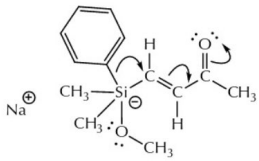
3.03 For over 200 years, a naturally occurring plant substance has been used to treat people with congestive heart failure. The biologically active compound is know as Ouabain (*J Org Chem*, **2003**, *68*, 2572), which helps to increase the force of cardiac muscle contraction. In a recent synthesis of Ouabain, the chemists carried out the following reaction.

Given that silicon (Si) atoms can behave as Lewis acids to achieve a 10-electron expanded shell configuration:
(i) draw the structure of the compound that can react with sodium methoxide ($NaOCH_3$) to give the product shown below; and
(ii) show the curved arrow mechanism that describes the reaction between this compound and sodium methoxide in order to give this product.

(iii) the curved arrows for the next step in the mechanism are shown below, draw the resulting ionic compound



3.04 Silicon atoms can behave as Lewis acids to achieve expanded shell electron configurations. In question 3.03, above, an example of a 10-electron silicon atom is shown. There are additional expanded shell configurations that are possible for silicon, and other atoms, with > 10 electrons. For example, silicon tetrafluoride (SiF_4) is observed to react with two equivalents of sodium fluoride (NaF) to give a single, new, ionic compound. Using complete Lewis structures, provide the full chemical equation for this stepwise reaction, including the curved arrow notation.

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3.2 Brønsted Acid-Base Reactions

A. Reactivity of Brønsted Acids and Bases

The Lewis acid-base model is not the only one that exists, and it was not the first. Identifying the properties associated with "acids" (sharp, acrid taste) and "bases" (bitter taste; slippery feeling) has been around for a long time, and both of the words were in common use by the late 1700s.

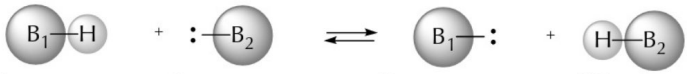
Svante Arrhenius proposed an ionic model for acids and bases in the 1880s (acids increase the concentration of H^+ ions and bases increase the concentration of HO^- ions), which was still decades before subatomic particles were discovered. In the 1920s, with the electronic model of bonding becoming firmly established, Johannes Brønsted and Thomas Lowry refined the Arrhenius idea to a specific reactivity, namely, the proton transfer reaction.

A general outline for the proton transfer reaction is shown in Figure 0306.

Figure 0306

The defining terms in Brønsted acid-base reactions.

Brønsted acid-base chemistry: the proton transfer reaction



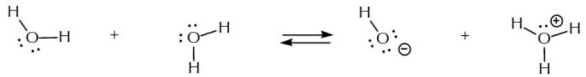
B_1-H
a Brønsted acid is a base (B_1) sharing an electron pair with a proton

:B_2
a Brønsted base is an atom (B_2) with an electron pair it can share with a proton

:B_1
the deprotonation of B_1-H creates :B_1, the conjugate base of B_1-H

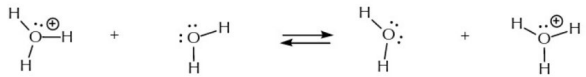
H-B_2
the protonation of :B_2 creates B_2-H, the conjugate acid of :B_2

Water as a Brønsted acid and water as a Brønsted base (outcome: hydroxide and hydronium ions)



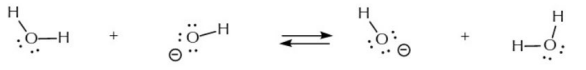
change in charges
acid: 0 -> -1
base: 0 -> +1

Hydronium ion as a Brønsted acid and water as a Brønsted base (outcome: water and hydronium ion)



change in charges
acid: +1 -> 0
base: 0 -> +1

Water as a Brønsted acid and hydroxide ion as a Brønsted base (outcome: hydroxide ion and water)



change in charges
acid: 0 -> -1
base: -1 -> 0

The definition of a Brønsted acid is a proton donor, while the Brønsted base is a proton acceptor. Hence, the "proton transfer reaction" is the movement of a proton (H^+) from the Brønsted acid to the Brønsted base.

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Any reacting partner containing a hydrogen atom that is covalently bonded to any other atom is a potential Brønsted acid. Referring to Figure 0306, in the structure of a Brønsted acid (B_1-H), the proton donor, can be viewed equivalently as a Brønsted base (B_1:), to which a proton is attached. This Brønsted base (B_1:), which is embedded in the Brønsted acid (B_1-H), is called the conjugate (companion) base of the original Brønsted acid.

Any reacting partner containing an atom with an electron pair with which to form a new covalent bond with a hydrogen ion is a potential Brønsted base. The structure of a Brønsted acid (:B_2), the proton acceptor, can be viewed equivalently as then forming a Brønsted acid (H-B_2) upon its bonding with a proton. This new Brønsted acid (H-B_2), which forms from the Brønsted base (:B_2), is called the conjugate (companion) acid of the original Brønsted base.

Because a proton is positively charged, the charge on the conjugate base of the original Brønsted acid will diminish by 1 (-1) when the proton is removed. Correspondingly, the charge on the original Brønsted base will add 1 (+1) when it bonds with the proton. This consistent change can be seen in the three specific examples of proton transfer reactions included in Figure 0306, featuring combinations of water, hydronium ion, and hydroxide ion.

Every covalent bond involving a hydrogen atom is a potential Brønsted acid. The difference in Brønsted acidity between all of those bonds is how likely or unlikely the bond can be broken to transfer the proton, and so exhibit the property of its Brønsted acidity.

Similarly, every nonbonding electron pair can, in principle, form a new bond with a proton, and so the atom carrying the nbe pair is a potential site of a Brønsted base. How relatively readily the electron pair can be shared is the property of its Brønsted basicity.

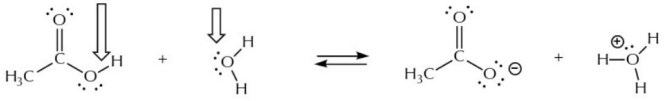
The discussion about these examples, as well as those in Figure 0307, is focused on introducing the different and complementary ways that the language of Brønsted acid-base chemistry is used. There are synonymous ways to say exactly the same thing, and these all boil down to the same single phenomenon: a proton is transferred between two atoms, each bearing an electron pair for forming a covalent bond with the proton during the competition over which one ends up bonded to it.

Two more representative Brønsted acid-base reactions are illustrated in Figure 0307.

Figure 0307
Representative Brønsted acid-base reactions.

The proton transfer reaction between acetic acid and water

OH bond of acetic acid breaks when the nbe pair of the oxygen atom in water bonds to that hydrogen atom



acetic acid acting as a Brønsted acid, is deprotonated by water

water acting as a Brønsted base, deprotonates the acetic acid

acetate ion: the deprotonated acetic acid is its conjugate base (i.e., the part of the molecule that had been holding on to the proton, originally)

hydronium ion: the conjugate acid of water (i.e., the protonated water molecule)

four equivalent expressions:
- acetic acid protonates water
- water deprotonates acetic acid
- acetic acid is deprotonated by water
- water is protonated by acetic acid

The proton transfer reaction between water and sodium hydride on next page . . .

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Figure 0307

Representative Brønsted acid-base reactions.

. . . Figure 0307 continued from previous page.

The proton transfer reaction between water and sodium hydride

water acting as a Brønsted acid, is deprotonated by the hydride ion

sodium hydride acting as a Brønsted base, the hydride ion deprotonates the water

sodium hydroxide: the deprotonated water; conjugate base of water

hydrogen gas: the protonated hydride ion; conjugate acid of hydride

four equivalent expressions:
- water protonates hydride ion
- hydride ion deprotonates water
- water is deprotonated by hydride ion
- hydride ion is protonated by water

On the left-hand side of the first chemical equation (see previous page; commonly "the reactants," or the "starting materials"), both of the molecules are potential Brønsted acids and bases. The acetic acid structure has 4 C-H bonds and 1 O-H bond (potential Brønsted acidic sites) and nbe pairs on both oxygen atoms (potential Brønsted basic sites). Water also has both features: 2 O-H bonds (acidic sites) and 2 nbe pairs (basic sites).

At this point in the discussion, you need the results to guide you in which of the possible proton transfer reactions has taken place, and this is found in the structures of the observed products and then comparing the two sides of the equation. Acetic acid is the Brønsted acid (the substance from which a proton is removed), and water is the Brønsted base (the substance that accepts the proton from acetic acid). The products of proton transfer are shown on the right-hand side of the equation and indicate this transfer. Acetate ion, which is formed by the loss of a proton from acetic acid, is the conjugate base of acetic acid, and the hydronium ion is the conjugate acid of water. Thinking about the reverse reaction (moving from the right- to left-hand side of the equation), the acetate ion can retrieve the proton from the hydronium ion to re-form acetic acid and water.

In the second equation, only water has a covalent bond involving a hydrogen atom, and so it is the only candidate with a potential Brønsted acid site. Sodium hydride is an ionic compound possessing the hydride ion. In this example, then, water is the Brønsted acid, and it is deprotonated by the hydride ion from sodium hydride, which is the only atom bearing a nbe pair to act as a Brønsted base. The products of the proton transfer reaction are hydroxide ion (the conjugate base of water) and hydrogen gas (the conjugate acid of hydride ion). In this reaction, the arrow is shown as a reaction on a one-way street. There is no opportunity for the hydroxide ion to take the proton back. The molecular hydrogen is a gas, and so it would bubble out of the reaction vessel. This is an example of how a reaction can shift completely to one side (in this case, towards the products) by the physical removal of one of the products from the reaction mixture. More generally, this is an example of Le Châtelier's Principle.

Read carefully the four statements associated with each of the examples in Figure 0307 listed as "four equivalent expressions." These statements are all synonymous ways of expressing the proton transfer reaction indicated by the structures.

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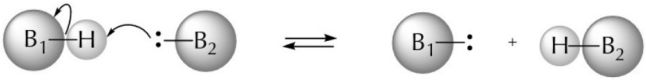
B. Curved Arrow Convention and the Organic Reaction Mechanism

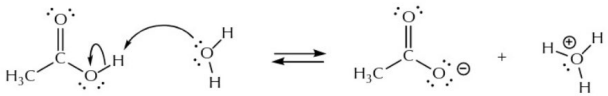
Representing the proton transfer reaction with the curved arrow convention shows that the bond breaking and bond making with respect to the proton are happening simultaneously (Figure 0308).

Figure 0308
The curved arrow mechanism for Brønsted acid-base reactions.

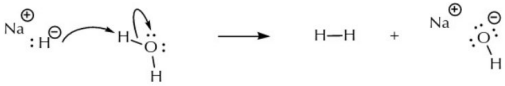
Brønsted acid-base chemistry: the proton transfer reaction mechanism



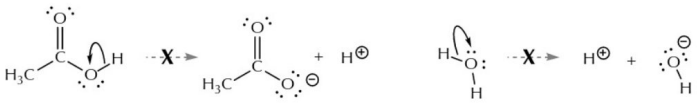
The proton transfer reaction mechanism between acetic acid and water



The proton transfer reaction mechanism between water and sodium hydride



of note: *no free protons*



Although the Brønsted acid-base reaction is called a proton transfer, note that at no point in these mechanisms do we draw free protons. The representation for what that would look like is shown at the bottom of Figure 0307. You will encounter many places, such as texts and internet resources, where free protons are used, and these drawings should not be taken literally… their authors do not mean it! They mean: a proton source acting as a Brønsted acid.

Drawing free protons is a convenient shorthand, but it takes away from the experimental fact that the proton transfer reaction is an actual chemical reaction that requires the collisions of molecules. Underlying the question of free protons is an interesting debate that you will also encounter: Are Brønsted acids also Lewis acids?

As is true for any scientific, sociological, or aesthetic debate, there is no absolute and discoverable answer to this question. What exists are the arguments for defending one position versus another, and the value that you end up putting on the relative strengths of the arguments based on the evidence (including what counts as evidence).

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C. Are There Free Protons in a Reaction Flask? The Lewis Versus Brønsted Acid Debate

In this text, we will adhere to the idea that free protons (H^+) do not exist in any practical chemical sense and should not be drawn. This position is supported by the experimental observation that free protons only exist under extreme conditions (such as high temperatures and in interstellar space), but never under typical laboratory conditions, such as in a reaction flask. This section further discusses how the lack of free protons can then influence drawing acid-base mechanisms and for the definitions of terms in acid/base reactions.

We need to look to the field of physics for what is known about free protons, and we learn the following experimental facts:

(a) Free protons are observed at temperatures high enough to separate them from nearby electrons and/or other subatomic particles and form a plasma, which is a gas made up of ions (10–30,000 K, about the same temperature of the relatively "cooler" sunspots on the surface of the sun).
(b) Cosmic rays, originating from the sun, are mainly high energy protons.
(c) Radioactive decay of neutrons can create free protons with extremely short lifetimes.

A delightful experimental fact from chemistry is also relevant to the story of whether free protons exist. In the 1920s, while trying to study the chemistry of high energy protons, researchers were using the extremely inert noble gas helium, figuring that it could not interact chemically and bond with anything else. They observed direct experimental evidence for the HeH^+ ion (protonated helium). It is so unlikely to see a free proton when any source of electrons is present that even helium can act as a Brønsted base when there is no better option present. The HeH^+ ion has been studied in depth over this past century and has been observed in interstellar space.

Many Brønsted acids act as though they are providing protons freely, and so the tendency to draw them might derive from that behavior. In general, the rate of proton transfer in solutions is fast (10^7–10^9 per second, per unit volume), which approaches the number of collisions taking place in a solution, in general (10^{10} per second, per unit volume). In other words, when there are proton transfers that can take place, they occur about 1 in every 10–1,000 times that two molecules collide, and those collisions are happening incredibly fast and frequently. In water, a proton from a hydronium ion is being transferred rapidly from water molecule to water molecule ($H_3O^+ + H_2O \rightarrow H_2O + H_3O^+$, and so on).

But: a mechanism is the story that we tell for what we think is happening at the molecular level, and there is a huge difference between (a) thinking that the open shell proton is free, floating around, and available as a reactant versus (b) thinking that a proton always needs to be bound to an atom from which it is removed in a collision.

The bottom line: There is no evidence, under the normal operating conditions in a chemical laboratory, that you will have free protons in your reaction flask. This fact governs how you draw the mechanism of a Brønsted acid-base reaction. Throughout this text, we will maintain, even when not sure of the proton source, that it is always better to write "H-B" than it is to write "H^+" when drawing out a mechanism, because that is a better story about the chemical reaction (i.e., no free protons in the flask).

We turn now to the Lewis and Brønsted definitions of acids and bases, and whether the definitions overlap or not. This topic is always taken up in texts and web pages where the relationship between the Lewis and Brønsted models for acids is discussed.

Comparing Brønsted and Lewis bases. There is widespread agreement that the terms "Lewis base" (electron pair donor) and "Brønsted base" (proton acceptor) are synonyms. To accept a proton (Brønsted base), a molecule needs an electron pair (Lewis base) to form a new covalent bond with a proton.

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Comparing Brønsted and Lewis acids. There is still debate in the chemistry community about whether Brønsted acids are also Lewis acids, and whether these two categories are identical or absolutely do not overlap. And, because you will see references to both conclusions and because acid-base topics are so prevalent in chemistry and biochemistry, the rest of this section is devoted to highlighting this debate.

There are three different arguments in the Brønsted versus Lewis debate.

Argument #1: The free proton exists, and all Brønsted acids are also Lewis acids. There are free proton advocates. And, as described above, free protons do exist, but only under extreme conditions, and not in a normal chemical laboratory setting. Yet even in the Wikipedia entry under Lewis acids, the authors hedge their bet. In one spot, it says "The description of a Lewis acid is often used loosely. For example, in solution, bare protons do not exist." And then, a bit later "The proton (H^+) is one of the strongest but is also one of the most complicated Lewis acids. It is convention to ignore the fact that a proton is heavily solvated (bound to solvent). With this simplification in mind…"

The conclusion from the free proton argument is convenience: All Brønsted acids are Lewis acids because they are proton sources and thereby open shell atoms, even if the free proton does not actually exist in chemical reactions; it is a convenient shorthand.

Argument #2: The free proton does not exist, but all Brønsted acids are also Lewis acids because an electron pair is "accepted" by the acid. When HCl gets deprotonated by a Brønsted base, the hydrogen atom of the HCl has acted as an electron pair acceptor while, at the same time, losing the electron pair from the HCl bond, which needs to break at the same time. The HCl molecule is assigned the role of the Lewis acid. There is no net gain of a bond, a criterion that goes back to the original formulation by Lewis when chemical bonds were thought of as being made from ions.

The conclusion here is also that all Brønsted acids are Lewis acids because the acids are deemed as "accepting" an electron pair during the collision, even if another bond needs to break at the same time.

Argument #3: The free proton does not exist, and Brønsted acids are never Lewis acids. When the Brønsted acid, HCl, reacts with a base, a new bond is formed and the old bond is broken. The acid is not accepting an electron pair, in the Lewis sense, as much as it is swapping one pair for another. The hydrogen atom is not open shell, and no net electron gain (a bond) takes place, as in the reactions of open shell atoms.

The conclusion here is that Brønsted acids are not Lewis acids.

While these are interesting debates, we think that the third argument is the most defensible because it makes a useful chemical distinction between the open shell atoms (boron, aluminum, etc.) of Lewis acids and the proton transfer reactions of Brønsted acids. In the chemistry of open shell atoms, a new bond is formed (as in a complexation), and this is a useful chemical distinction from the Brønsted acid-base reaction, which combines a bond-breaking process with its bond-forming process.

In the end, these different arguments do not end up with different results: Protonation takes place. The question is: how? And in mechanistic chemistry, we are absolutely interested in the story about how the bonding changes take place, the timing of the events at the molecular level, and best ways to draw and describe chemical processes.

Our positions on the free proton and Brønsted-Lewis debate are:

(1) There are no free protons in chemistry, so draw H-B or the actual acid and never H^+.
(2) Lewis acids are open shell atoms that accept a Lewis base to form a new bond, and Brønsted acids derive from covalently bonded hydrogen atoms, so there is no overlap in these two classifications.
(3) Lewis bases and Brønsted bases are identical classifications.

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The following passage, from a text on chemistry and physiology of the liver, contains exactly the same caution addressed to clinicians:

> The term "hydrogen ion concentration" has infuriated some chemists for a variety of reasons. First, although it is biologically meaningful to talk about the concentration of large molecules such as serum albumin (molecular weight of 65,000 g) that have a measurable dimension, it does not appear to be useful to express hydrogen ion as a concentration.
>
> The reason is that the hydrogen ion is unique, in that it consists only of a proton without an accompanying electron shell and is therefore orders of magnitude smaller than other ions in [blood] plasma. Second, the proton does not exist as its own entity in water; instead, the hydronium ion (H_3O^+) is its most prevalent form.
>
> In other words, even if it were biologically meaningful to express protons in terms of concentration, the term "hydrogen ion concentration" would be a misnomer, and "hydronium ion concentration" more correct.
>
> P Constable, "Clinical Acid-Base Chemistry." In C Ronco, R Bellomo, JA Kellem, eds., *Critical Care Nephrology, 2E.*, Philadelphia: Elsevier/Sanders, **2009**, 581.

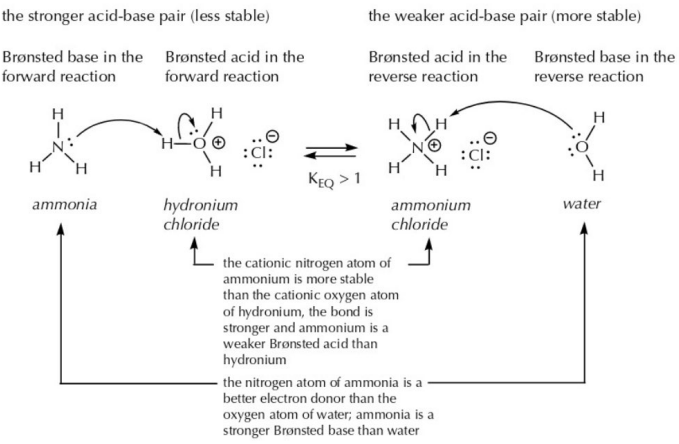
D. Evaluating the Position of the Brønsted Acid-Base Equilibrium

In Section 3.1D, examples of using fundamental structural principles to evaluate the position of Lewis acid-base reactions are shown, including (a) atom identity (position on the periodic table), (b) hybridization, (c) delocalization, (d) closed shell atoms, (e) position of formal charge(s), and (f) the general molecular structure. For comparable examples, when there is only one structural difference between the acids and bases or when multiple differences are aligned towards the same conclusion, making predictions based upon principles generally works well.

For example, in the reaction of ammonia with hydronium ion, ammonia and water are the bases in competition for the proton (Figure 0309).

Figure 0309

The Brønsted acid-base reaction between ammonia and hydronium chloride.


the stronger acid-base pair (less stable)
the weaker acid-base pair (more stable)
Brønsted base in the forward reaction
Brønsted acid in the forward reaction
Brønsted acid in the reverse reaction
Brønsted base in the reverse reaction
$K_{EQ} > 1$
ammonia
hydronium chloride
ammonium chloride
water
the cationic nitrogen atom of ammonium is more stable than the cationic oxygen atom of hydronium, the bond is stronger and ammonium is a weaker Brønsted acid than hydronium
the nitrogen atom of ammonia is a better electron donor than the oxygen atom of water; ammonia is a stronger Brønsted base than water

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Their relative strengths of the two bases determines where the equilibrium lies. The nitrogen atom in ammonia and the oxygen atom in water are both (a) uncharged, (b) sp^3, (c) in comparable structural environments, including that their nbe pairs are localized. The position of this equilibrium can be evaluated by thinking about the Brønsted base strength as the ability to donate an electron pair to form a new bond. Because the nitrogen atom (ammonia) is less electronegative than the oxygen atom (water), it is more likely to share its electrons and would be deemed as a stronger base. Similarly, you can compare the structures of the two acids, ammonium and hydronium. The cationic nitrogen atom is easier to form (more stable) than the cationic oxygen atom, also due to nitrogen's lower electronegativity, and so the N-H bond is less likely to break to release a proton than the more polar O-H bond, making it a weaker acid.

Thus, the nitrogen atom's singular property, its greater propensity to share its electrons, is common to both its greater base strength (ability to share its electrons in forming a new bond with a proton) and the weaker acid strength of its conjugate acid (its bond to a proton is stronger than that of oxygen and can more easily be positively charged). Because nitrogen is less electronegative than oxygen, its covalent N-H bond is less polar covalent and involves a better sharing of the electrons than in an O-H bond. The electrons are already more unequally shared in the more polar covalent O-H bond, so its deprotonation occurs more readily than in the comparable N-H bond.

The protonation of a stronger base results in a weaker conjugate acid for exactly the same reason: The electrons are shared more readily (stronger base = a covalent bond with better electron sharing is formed with a proton), and this less polar covalent bond is less likely to break (weaker acid = a less polar covalent bond is harder to deprotonate). The reaction in Figure 0309 lies to the right-hand (products) side, $K_{EQ} > 1$, because ammonium ion is the weaker acid (the charge is more stable and the bond is more nonpolar covalent, on the nitrogen atom) and because water is the weaker base (the nbe pair is more stable, and less readily shared, on the more electronegative oxygen atom).

An atom that is less electronegative than nitrogen, rather than more electronegative, should show the same trend but result in nitrogen as the weaker base, and this is true. Carbon is less electronegative than nitrogen, and in comparable Brønsted acid-base pairing, the less electronegative carbon anion is a stronger base than its nitrogen atom counterpart (Figure 0310). The conjugate acid of the carbon base (butane) is a weaker acid than the one derived from the nitrogen base (1-propanamine).

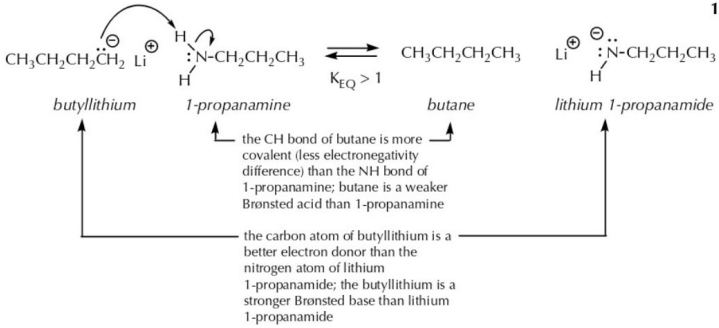
the stronger acid-base pair (less stable)
the weaker acid-base pair (more stable)
Brønsted base in the forward reaction
Brønsted acid in the forward reaction
Brønsted acid in the reverse reaction
Brønsted base in the reverse reaction
$CH_3CH_2CH_2\ddot{C}H_2$ Li
H
:N-$CH_2CH_2CH_3$
H
$K_{EQ} > 1$
$CH_3CH_2CH_2CH_3$
Li
:N-$CH_2CH_2CH_3$
H
butyllithium
1-propanamine
butane
lithium 1-propanamide
the CH bond of butane is more covalent (less electronegativity difference) than the NH bond of 1-propanamine; butane is a weaker Brønsted acid than 1-propanamine
the carbon atom of butyllithium is a better electron donor than the nitrogen atom of lithium 1-propanamide; the butyllithium is a stronger Brønsted base than lithium 1-propanamide

Figure 0310
The Brønsted acid-base reaction between butyllithium and 1-propanamine.

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Figure 0311

The Brønsted acid-base reaction between sodium phenoxide and ethanol.

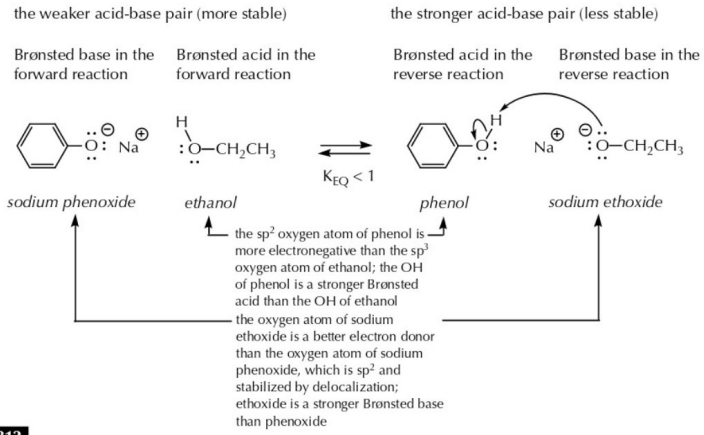
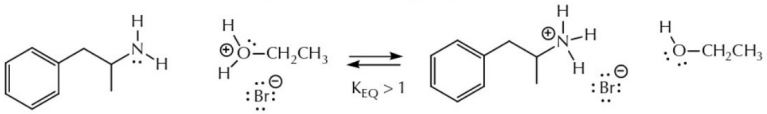

the weaker acid-base pair (more stable)
the stronger acid-base pair (less stable)
Brønsted base in the forward reaction
Brønsted acid in the forward reaction
Brønsted acid in the reverse reaction
Brønsted base in the reverse reaction
$K_{EQ} < 1$
sodium phenoxide
ethanol
phenol
sodium ethoxide
the sp^2 oxygen atom of phenol is more electronegative than the sp^3 oxygen atom of ethanol; the OH of phenol is a stronger Brønsted acid than the OH of ethanol
the oxygen atom of sodium ethoxide is a better electron donor than the oxygen atom of sodium phenoxide, which is sp^2 and stabilized by delocalization; ethoxide is a stronger Brønsted base than phenoxide

Figure 0312

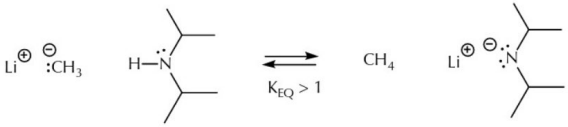
Brønsted acid-base reactions between molecules that are analogous to previous examples.

a Brønsted acid-base reaction analogous to the one in **Figure 0309**

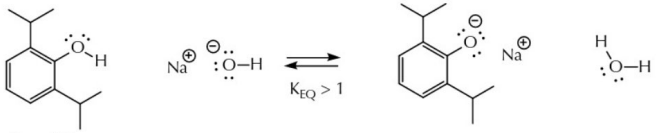


amphetamine

a Brønsted acid-base reaction analogous to the one in **Figure 0310**



a Brønsted acid-base reaction analogous to the one in **Figure 0311**



Propofol

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Many other comparisons are possible. In the examples in Figure 0311, the more electronegative sp^2 oxygen atom in phenol makes its OH bond more acidic than the OH bond on the sp^3 oxygen atom of ethanol. And the delocalized sp^2 oxygen anion in the phenoxide base is more stable (less basic) than the sp^3 oxygen anion of the ethoxide ion.

By analogy, organic molecules that are structurally similar to any of the molecules in the previous examples will show a comparable pattern of reactivity. This ability to make structural analogies and predict reactivity is a powerful feature of organic chemistry. Replacing hydrogen atom groups with saturated hydrocarbon groups does not strongly affect the predicted reactivity (Figure 0312).

As illustrated with Lewis acids and bases in Section 1.3D, the competition between atoms in the same structure can sometimes be evaluated using fundamental structural principles. Between the two uncharged, sp^3 oxygen and nitrogen atoms, the strong Brønsted base (the less electronegative nitrogen atom) is more likely to be protonated by the strong Brønsted acid HCl (hydrochloric acid) than the oxygen atom (Figure 0313). All of the standard criteria for evaluating molecular stability need to be considered when evaluating these acid-base reaction products, and they are not ranked: period/size, closed shell atoms, charges, charge placement, and charge proximity including delocalization. The only difference here is the placement of the positive charge on the less electronegative (and more basic) nitrogen atom, which is more stable than when the positive charge is on the more electronegative (and less basic) oxygen atom.

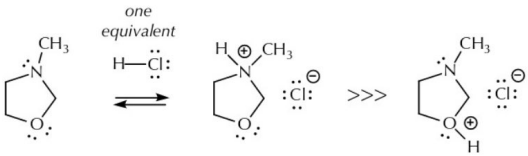

Figure 0313
Competitive selectivity between different Brønsted bases in the same molecule.

	N^+ versus	O^+
period	2nd row	2nd row
hybridization	sp^3	sp^3
delocalizable	no	no
all closed shell	yes	yes
formal charges	+1	+1
structure	hydrocarbon	hydrocarbon
charge placement	+ on N	+ on O

In the last example in this section (Figure 0314), both of the oxygen atoms are uncharged and sp^2 hybridized. Protonation of the oxygen atom of the carbon-oxygen double bond (O_1) creates a positive charge than can be stabilized by delocalization, while the conjugate acid of the other oxygen atom (O_2) cannot be stabilized in the same way. Yet, the protonated O_2 atom is sp^3 hybridized, which is a less electronegative hybridization, and would be favored over the positive charge on the more electronegative sp^2 oxygen atoms, and so the assessment criteria are not cleanly in one direction over another. The resolution, naturally, is derived from the experimental outcome: Protonation of the oxygen of the CO double bond is observed, while the protonation at the other oxygen atom is not.

The conclusion here is that the oxygen atom of the CO double bond is more basic (has a more favorable conjugate acid) than the other oxygen atom, and that the stabilization of the positive charge by delocalization is likely the most important criterion in explaining the observed reactivity.

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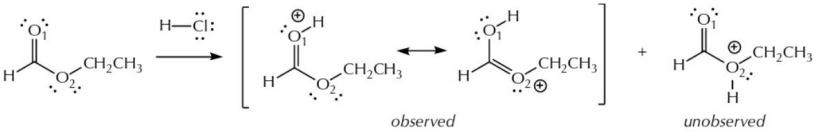
Figure 0314

Delocalization of charge in the conjugate acid can affect the relative basicity of atoms.



	O_1^+ versus	O_2^+
period	2nd row	2nd row
hybridization	sp^2	sp^3
delocalizable	yes	no
all closed shell	yes	yes
formal charges	+1	+1
structure	hydrocarbon	hydrocarbon
charge placement	+ on O_1/O_2	+ on O_2

So far in this chapter, in both the Lewis acid and Brønsted acid examples, making predictions based on fundamental principles is sometimes complicated because there are a number of criteria to consider and they are in competition. In fact, most of the examples, so far, have been carefully selected so that predictions can be made. More often, the various structural features (charge, hybridization, delocalization, etc.) do not clearly favor one of the reactive sites over the other.

Although it would be wonderful if true, experimental results show that it is not possible to rank the structural features in relative importance, so a comprehensive predictive model does not exist. Sometimes the charge matters more than delocalization; sometimes less. As a result, the only generally reliable way to evaluate relative acid-base strength is to use experimentally determined results. This topic, using experimental results and making analogies from them, is important enough to take up the remaining parts of this chapter.

As a final note, it is worthwhile pointing out that the language about the position of the acid-base equilibrium can appear counterintuitive. When we think about "strength" we often think about ideas of persistence and survival, and about the one who wins in a competition. In an acid-base contest, the weak acid-base pair is the survivor.

The definition of a strong Brønsted acid, as the better proton donor, is an inherently self-destructive one: The strong acid is the one where the bond breaks, and so the one there is the least of when the reaction reaches equilibrium. The bond to the hydrogen atom in the strong acid is more polar, which is why it is a better proton donor. There is more of the weaker acid present when the reaction is complete because the bond to the hydrogen atom is more nonpolar, with more covalent (sharing) character, which is why it is a poorer proton donor.

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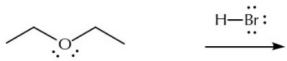
PRACTICE QUESTIONS

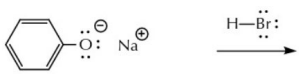
3.05 Provide the structure of the conjugate acids for the following compounds. Use HBr as the Brønsted acid and be sure to give the balanced equation.

(a) diethyl ether

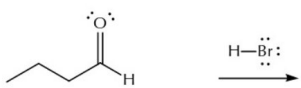


(b) 2,6-dimethylpyridine

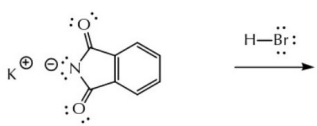
(c) sodium phenoxide



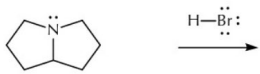
(d) butanal



(e) potassium phthalimide



(f) pyrrolizidine



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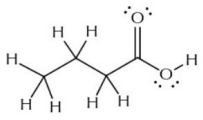
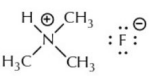
3.06 Provide the structure of the conjugate bases for the following compounds. Use CH_3Li as the Brønsted base and be sure to give the balanced equation.

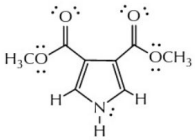
(a) butanoic acid



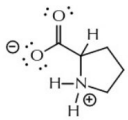
(b) trimethylammonium fluoride



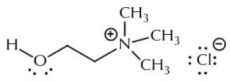
(c) dimethyl 3,4-pyrroledicarboxylate



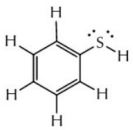
(d) proline



(e) choline



(f) thiophenol



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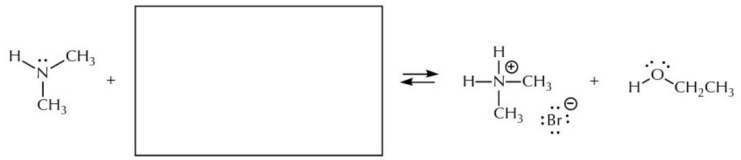
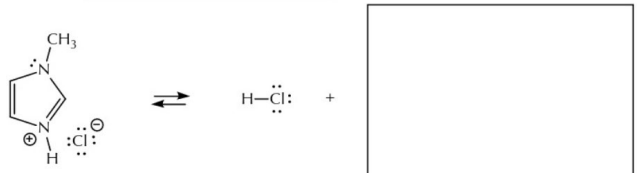
3.07 Each of the following is a Brønsted acid-base reaction. Use the information present to deduce the structure of the missing reagent.

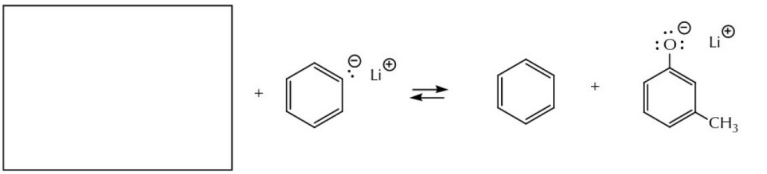
(a)



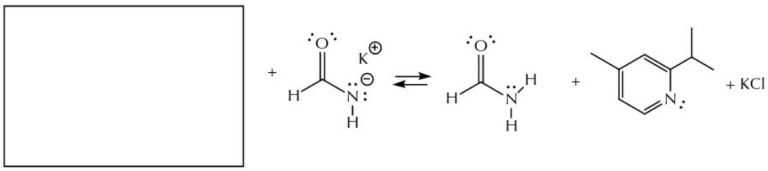
(b)



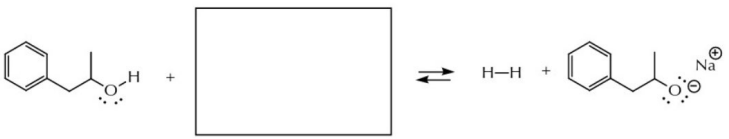
(c)



(d)



(e)



3.08 In the 5 examples in question 3.07, fundamental principles can be used to predict whether the equilibrium constant will be greater than 1 or less than 1. Make the prediction.

(a) ☐ (b) ☐ (c) ☐ (d) ☐ (e) ☐

3.09 In the 5 examples in question 3.07, provide the curved arrow notation for the mechanisms of the forward reactions.

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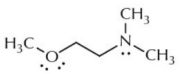
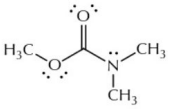
3.10 Sulfuric acid [H_2SO_4; connectivity $(HO)_2SO_2$] is a strong Brønsted acid. Each of the following molecules has two or more potentially Brønsted basic atoms, and one of them is signficantly more basic than the other(s). Using just fundamental principles to make the selection, provide structures for the most favorable (stable) Brønsted acid-base reaction product anticipated for each of the following molecules, and briefly indicate the reason for the choice.

(a)



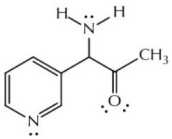
reaction product with H_2SO_4	explanation

(b)



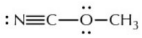
reaction product with H_2SO_4	explanation

(c)



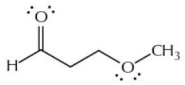
reaction product with H_2SO_4	explanation

(d)



reaction product with H_2SO_4	explanation

(e)



reaction product with H_2SO_4	explanation

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3.3 The Quantitative Scale for Brønsted Acidity

A. Which Acid Is Stronger?

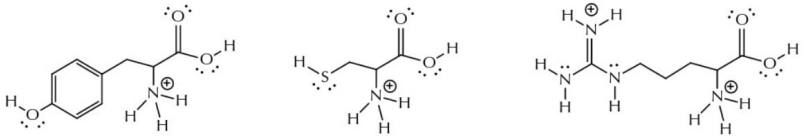
In the first two sections of this chapter, some carefully selected examples were used so that you could predict, based on fundamental principles such as differences in electronegativity, charge, or delocalization of charge, which of a pair of molecules was the stronger acid (or base).

In millions of the other organic compounds that have been discovered, there are competitions between multiple structural features used for making predictions about relative acid-base strength, and a table with millions of entries is neither practical nor useful. Fortunately, there is a way out of this dilemma. Organic compounds have recurring combinations of structural features and, with enough representative examples, patterns of reactivity are observed, and good predictions can be made by creating analogies.

For example, the class of compounds known as amino acids, which are the fundamental building blocks for making protein molecules, have at least two and sometimes three potentially acidic functional groups. Three of these amino acids, each with multiple available Brønsted acidic sites, are shown in Figure 0315.

Figure 0315

Three amino acids with multiple Brønsted acidic sites in each.



tyrosine *cysteine* *arginine*

All three of these molecules present the same dilemma for making a prediction from fundamental principles. The O-H bonds on the right-hand side of the three structures are on uncharged, sp^2 oxygen atoms for which delocalization is possible. All three compounds also have positively charged, sp^3 nitrogen atoms with no possible delocalization. Even without the other functional groups, making a principled prediction is not obvious: is the N-H going to be the stronger acid because deprotonation of the cationic nitrogen atom is more favorable, or is the O-H going to be the stronger acid because the oxygen atom is more electronegative, including its hybridization, and has delocalizable electrons? This is a question that needs to be answers experimentally.

Each of the compounds has one other functional group, plus a collection of C-H bonds. Tyrosine has another sp^2 oxygen atom on the benzene ring for which delocalization is also possible. Cysteine has an S-H bond. And arginine has a positively charged group with multiple, sp^2 nitrogen atoms for which delocalization is possible.

Ranking the strengths of the Brønsted acids in tyrosine, cysteine, and arginine, both within the structures, or between the different molecules, cannot be done based on a single, isolated structural feature because the various features are combined. Factors that both favor and disfavor the Brønsted acidity are present in all of them. Consequently, a quantitative scale for acid strength was developed, so that the experimental results could be used to answer the question "Which acid is stronger?"

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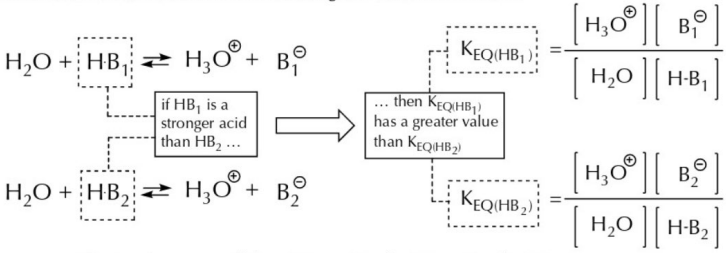
B. A Quantitative pK_a Scale Based on Dissociation of Acids in Water

The standard acidity scale uses water as the point of reference. The equilibrium constant for the reaction between any Brønsted acid and water is used to define its acidity (Figure 0316). If HB_1 is a stronger Brønsted acid than HB_2, then the K_{EQ} for the reaction of HB_1 with water will be greater than the K_{EQ} for the reaction of HB_2 with water.

Figure 0316

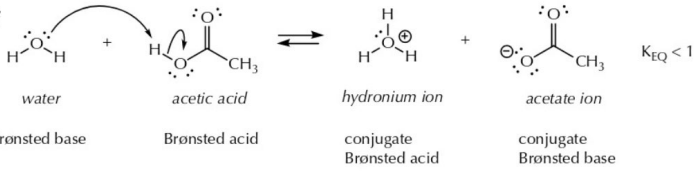
The relative acidities of Brønsted acids are measured against water as a reference.


$H_2O + HB_1 \rightleftharpoons H_3O^{\oplus} + B_1^{\ominus}$
$K_{EQ(HB_1)} = \frac{[H_3O^{\oplus}][B_1^{\ominus}]}{[H_2O][H\text{-}B_1]}$
if HB_1 is a stronger acid than HB_2 ...
... then $K_{EQ(HB_1)}$ has a greater value than $K_{EQ(HB_2)}$
$H_2O + HB_2 \rightleftharpoons H_3O^{\oplus} + B_2^{\ominus}$
$K_{EQ(HB_2)} = \frac{[H_3O^{\oplus}][B_2^{\ominus}]}{[H_2O][H\text{-}B_2]}$
HB_1 is a stronger acid than HB_2
K_{EQ} for $HB_1 > K_{EQ}$ for HB_2

When acetic acid is dissolved in water (Figure 0317), an acid-base reaction occurs and fixed concentrations of acetic acid, water, acetate ions, and hydronium ions are present at equilibrium. Acetic acid is the acid on the right-hand side of the equation, and hydronium ion is the conjugate acid, on the right-hand side of the equation. As written, water is acting as the base, and acetate ion is the conjugate base. The measured equilibrium constant is a small, fractional value ($K_{EQ} < 1$), which means that the denominator in the equilibrium expression (the starting materials) are in higher concentration than the products (in the numerator), and the reaction lies substantially on the left-hand side. Chemically, this means that hydronium ion is a stronger acid than acetic acid, and that acetate ion is a stronger basic than water. The more persistent, weaker acid-base pair (acetic acid and water) are in higher concentration.

Figure 0317

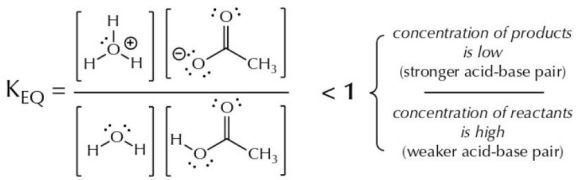
Dissociation of acetic acid in water.



The equilibrium constant for this reaction, K_{EQ}, as drawn in Figure 0317, is shown in Figure 0318.

Figure 0318

Equilibrium constant for the dissociation of acetic acid in water.


$K_{EQ} =$
< 1
concentration of products is low (stronger acid-base pair)
concentration of reactants is high (weaker acid-base pair)

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For dilute solutions, in which the concentration of water is a constant value (55.5 M; see Figure 0203), this concentration of water term $[H_2O]$ is combined with K_{EQ} to give another expression, the acidity constant, K_a. For acetic acid, the acidity constant is measured to be 1.75×10^{-5}, which is a small fraction, less than 1, and consistent with the idea that acetic acid is a weaker Brønsted acid than hydronium ion, so there is more of it at equilibrium (Figure 0319).

Figure 0319

The acidity constant for acetic acid.

$$K_{EQ}\,[H_2O] = K_a = \frac{\left[\text{H}_3\text{O}^{\oplus}\right]\left[\text{CH}_3\text{CO}_2^{\ominus}\right]}{\left[\text{CH}_3\text{CO}_2\text{H}\right]} = 1.75 \times 10^{-5} = \frac{1}{175{,}000}$$

The acidity constants for different acids have magnitudes ranging from 10^{14} (exceptionally strong) to 10^{-50} (exceptionally weak). To make using these numbers more convenient, they are tabulated as logarithms. As a reminder, the logarithm (log base 10, "$\log_{10}$" or just "log") of a number N is the exponent x in 10^x that equates to the number. That is, if N can be expressed as 10^x, then the $\log(10^x) = x$.

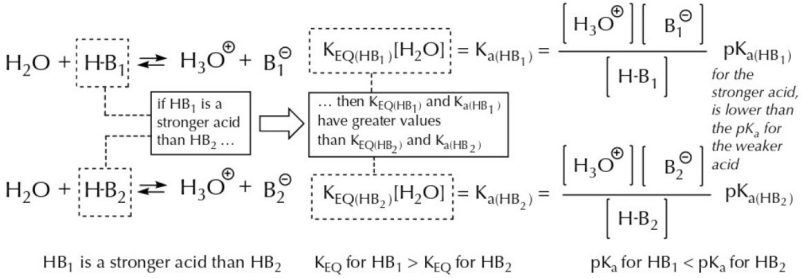
The log of the acetic acid acidity constant is -4.76:
i.e., $[\log(1.75 \times 10^{-5})] = [\log(1.75) + \log(10^{-5})] = [0.24 - 5.00] = -4.76$.

Just as pH is -log $[H_3O^+]$, so pK_a is defined as $-\log K_a$. The pK_a value for acetic acid is 4.76, a value that is typical of many organic acids. A strong inorganic acid such as sulfuric acid has a K_a of about 10^9 and a pK_a value of around -9. The pK_a value of hydronium ion is -1.7, while that of the ammonium ion is 9.4. Hydrocarbons, such as methane, are extraordinarily weak acids, with pK_a values of approximately 50. Inside the front cover of this book is a table of pK_a values for a variety of acids, shown with their conjugate bases. Fortunately, the familiar trend you would have learned for pH (lower pH value, more acidic environment) has its parallel in the pK_a values (lower pK_a value, stronger Brønsted acid).

The earlier figure (Figure 0316) can be revisited (Figure 0320): The stronger acid has the weaker conjugate base and the lower pK_a value. For example, the K_a for the stronger acid, HB_1, might be 10^4, while the K_a for the weaker acid, HB_2, is 10^{-3}. The pK_a for HB_1 ($-\log 10^4 = -4$) is lower than the pK_a for HB_2 ($-\log 10^{-3} = +3$). As exponents, you read the difference in pK_a values as "HB_1 is 10^7 times more acidic than HB_2."

Figure 0320

The relationship between acid strength, the acidity constant, and the pK_a value.


H2O + H-B1 ⇌ H3O⊕ + B1⊖
KEQ(HB1)[H2O] = Ka(HB1) = [H3O⊕][B1⊖] / [H-B1]
pKa(HB1)
for the stronger acid, is lower than the pKa for the weaker acid
if HB1 is a stronger acid than HB2 ...
... then KEQ(HB1) and Ka(HB1) have greater values than KEQ(HB2) and Ka(HB2)
H2O + H-B2 ⇌ H3O⊕ + B2⊖
KEQ(HB2)[H2O] = Ka(HB2) = [H3O⊕][B2⊖] / [H-B2]
pKa(HB2)
HB1 is a stronger acid than HB2
KEQ for HB1 > KEQ for HB2
pKa for HB1 < pKa for HB2

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Experimentally, only a relatively narrow range of pK_a values can actually be measured in water. Looking at simple saturated hydrocarbons, which are the weakest Brønsted acids, their pK_a values of about 50 means an equilibrium constant of around 10^{-50}. Even a mole of moles is "only" 10^{46} (10^{23} x 10^{23}), so one part in 10^{50} (in water) is an incredibly small number and not possible to measure. To get around these limits, measurements can be carried out in different solvents and then correlated back to water.

The pK_a table is a compilation of experimental values that provides a quantitative measure of acid strength. As you use the table, you will acquire a good sense of which acids are strong and which are weak, and you will become familiar with these representative values and how they correlate with organic chemical structures.

C. Reading Equations in Chemistry and Mathematics

For Brønsted acid HB, the defining equation for determining its acid strength, pK_a, is its reaction with water to give hydronium ions. A stronger Brønstead acid (HB) reacts with water to make more hydronium ion than a weaker acid makes (Figure 0321).

Figure 0321

As the acidity of HB increases, the reaction with water produces more hydronium ion.

$$H_2O + H\text{-}B \rightleftharpoons H_3O^{\oplus} + B^{\ominus}$$

the stronger HB is, the more the reaction with water lies to the right; the more this reaction lies to the right, the more hydronium ion is present and the larger the value of the equilibrium and acidity constants will be, and the lower the pK_a value will be

In a few mathematical steps, the relationship between pK_a values and pH values can be derived (Figure 0322). Historically, this equation resulting from this relationship was first derived by Lawrence Henderson, a noteworthy biochemist from the early 20th century, who used the equation to understand the physiology of acid-base chemistry and to use pH as a diagnostic tool. A few years later, Danish chemist Karl Hasselbalch, who first determined the pH of blood, transformed Henderson's equation into a logarithmic format.

Figure 0322

The relationship between pK_a values and pH values.

$$H_2O + H\text{-}B \rightleftharpoons H_3O^{\oplus} + B^{\ominus}$$

$$K_{EQ} = \frac{\left[H_3O^{\oplus}\right]\left[B^{\ominus}\right]}{\left[H_2O\right]\left[H\text{-}B\right]}$$

L Henderson, 1908

$$K_{EQ}\left[H_2O\right] = K_a = \frac{\left[H_3O^{\oplus}\right]\left[B^{\ominus}\right]}{\left[H\text{-}B\right]} \quad \textit{same as} \quad \left[H_3O^{\oplus}\right] = K_a\frac{\left[H\text{-}B\right]}{\left[B^{\ominus}\right]}$$

$$-\log K_a = -\log\left[H_3O^{\oplus}\right] - \log\left(\frac{\left[B^{\ominus}\right]}{\left[H\text{-}B\right]}\right)$$

K Hasselbalch, 1917

$$pK_a = pH - \log\left(\frac{[B^-]}{[HB]}\right) \quad \textit{same as} \quad pH = pK_a + \log\left(\frac{[B^-]}{[HB]}\right)$$

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This last equation proves to be quite useful, and it is called the Henderson-Hasselbalch equation.

> Every clinician dealing with acid-base abnormalities is familiar with the Henderson-Hasselbalch equation, probably the most famous equation in biology.
>
> The Henderson-Hasselbalch equation has proved invaluable in aiding the understanding of mammalian acid-base physiology and is routinely used in the treatment of acid-base abnormalities. With the traditional Henderson-Hasselbalch approach, the following primary acid-base disturbances have been defined: [respiratory and metabolic acidosis and alkalosis]
>
> P Constable, "Clinical Acid-Base Chemistry." In C Ronco, R Bellomo, JA Kellem, eds., *Critical Care Nephrology*, 2E., Philadelphia: Elsevier/Sanders, **2009**, 581.

In the Henderson-Hasselbalch equation, pK_a is being defined in terms of a pH, and a pH is a measurable quantity with a pH meter. So, reading the Henderson-Hasselbalch equation, in effect, describes an experiment for determining the pK_a value: If the log term is set to zero, then the pK_a value is equal to the measured pH.

How to set the log term to zero? Recall that the log 1 = 0; so, at the point where $[B^-] = [HB]$, the log $([B^-]/[HB])$ = log 1, and pK_a = pH. Experimentally, if you want to measure the pK_a value for a Brønsted acid HB, prepare a solution with a 1:1 mixture of HB and its conjugate base, B^-, then measure the pH. That pH value will be the pK_a value.

The pK_a value of an acid, HB, is the pH value of a solution when the concentrations of HB and its conjugate base are equal.

The following logical sequence should be understood by the relationships in the equations in Figure 0322:

> *As the acidity of HB increases… the amount of hydronium ion formed (in water) increases… the pH of the solution decreases… as does the corresponding pK_a value.*

Look at these two equivalent equations once again (Figure 0323). In the defining chemical equation, increasing the concentration of HB relative to its conjugate base should shift the equilibrium towards the right, increasing the concentration of hydronium ion, and lower the pH. Because the Henderson-Hasselbalch equation derives exactly from this chemical equation, you should be able to conclude exactly the same relationship from reading the mathematical equation as you do from the chemical equation.

The algebra is shown in the figure under three different $[HB]:[B^-]$ ratios.

$[HB]:[B^-] = 1:1$. As the second equation shows, at a 1:1 ratio of $[HB]:[B^-]$, the ratio in the log term is 1, and the evaluation of the log term is 0. The pH of the solution is defined only by the pKa value (which is a constant).

$[HB]:[B^-] = 10:1$. If you increase the concentration of HB, changing the $[HB]:[B^-]$ ratio from 1:1 to 10:1, you are increasing the amount of the acid form (HB), and that would shift the equilibrium (first equation) to the right, forming more hydronium ion. Forming more hydronium ion means that the pH of the solution decreases. The second equation says exactly the same thing (in fact, it must): If you change the $[HB]:[B^-]$ ratio from 1:1 to 10:1, the ratio in the log term goes from 1 to 1/10, and the evaluation of the log term goes from 0 to -1 (i.e., log 1/10 or log 10^{-1}). The negative of the log term is +1. Because the pKa is a constant, the pH value would need to go down by one unit (to pH = 3, the solution gets more acidic) when the -log term goes from 0 to +1.

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Figure 0323

Equivalent equations that relate pK_a with pH and the effect of changing the HB to B^- ratio on pH.

defining chemical equation for the acid strength of HB

$$H_2O + H\text{-}B \rightleftharpoons H_3O^{\oplus} + B^{\ominus}$$

relationship between pK_a and measurable quantitities

$$pK_a = pH - \log\left(\frac{[B^-]}{[HB]}\right)$$

HB pK_a = 4; [HB] = [B^-]

4 ⇨ $pK_a = pH - \log\left(\frac{[B^-]}{[HB]}\right)$ ⇨ 1

a constant

⇩

pH = 4 ⇦ log (1) = 0

(pK_a + (0))

HB pK_a = 4; increase [HB] > [B^-], 10:1, pH <

4 ⇨ $pK_a = pH - \log\left(\frac{[B^-]}{[HB]}\right)$ ⇨ 1/10

a constant

⇩

pH = 3 ⇦ log (1/10) = -1

(pK_a + (-1))

HB pK_a = 4; decrease [HB] < [B^-], 1:100, pH >

4 ⇨ $pK_a = pH - \log\left(\frac{[B^-]}{[HB]}\right)$ ⇨ 100/1

a constant

⇩

pH = 6 ⇦ log (1/10) = +2

(pK_a + (+2))

[HB]:[B^-] = 1:100. If you decrease the concentration of HB, changing the [HB]:[B^-] ratio to 1:100, you are decreasing the amount of the acid form (HB), and that would shift the equilibrium (first equation) to the left, diminishing the amount of hydronium ion. Decreasing the concentration of hydronium ion means that the pH of the solution increases. The second equation says exactly the same thing: If you change the [HB]:[B^-] ratio to 1:100, the ratio in the log term goes to 100:1, and the evaluation of the log term +2 (i.e., log 100/1 or log 10^2). The negative of the log term is -2. Because the pK_a is a constant, the pH value would need to go up by two units (to pH = 6, the solution gets more basic) when the -log term goes from 0 to -2.

There are four important quantitative relationships derived from pK_a values that can be used in organic chemistry: (a) predicting pK_a values for unknown compounds, (b) predicting the outcome of an acid-base reaction, (c) estimating of the magnitude of the position of an acid-base reaction, and (d) determining what structures are in solution at a given pH. These topics are all introduced in Section 3.4.

Before getting into those topics, we revisit in detail, in the next section, the various structural features that you need to pay attention to in organic molecules (atom identity, hybridization, charge, delocalization, etc.) and how these trends map out on the experimentally determined pKa values.

A small but representative subset of these molecules, and their pK_a values, comprise any pK_a table you might encounter (such as the one on the inside front cover). You will learn to use pK_a tables as a critical reference resource for predicting the acid-base properties of any organic compound you encounter.

D. Structural Trends and Brønsted Acidity

The pK_a table in this or any other book is as convenient as it is necessarily incomplete. With over 12 million known organic compounds, and only a fraction of them with their pK_a values determined experimentally, chemists use a representative sample of known pK_a values to estimate the acid-base strength of

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a vast array of molecules for which the data are unknown. The pK_a table in this text has about 40 molecules that range in acid strength with over a 10^{60} difference from the weakest pK_a 50) to the strongest (pK_a -12). Even a quick glance at the structures shows that what is nominally the same bond (e.g., OH) can range from pK_a -9 to pK_a 17.

By measuring a large number of pK_a values, two important conclusions are possible:

(1) a diverse set of structural features can affect the pK_a value, but in cases where only one of the usual structural features is operating (e.g., hybridization, atomic size), the trends in acid strength can often be predicted by applying general chemical principles; and

(2) although this diverse set of structural features that can affect pK_a are unranked, when the same set of features is present in two different molecules, the observed pKa values are comparably close.

The trends among main categories of structural features are useful to learn: atom identity, charge, hybridization, atomic size, and delocalization. This set provides a framework for analyzing the features of new and unfamiliar molecules whose pK_a you need to estimate. The five categories are not ranked in their importance, so the relative importance of feature one can vary from one combination to another.

Atom identity (in a row): As the electronegativity of B in HB increases, the bond is more polar, and the acidity of the HB bond increases (pK_a decreases); the basicity of a more electronegative atom is less than a less electronegative atom as its electrons are less likely to be shared.

As in the earlier examples of predicting the most favorable outcomes from Lewis and Brønsted acid-base reactions (Sections 3.1D, 3.2D), when a comparison is between atoms in the same row (and their charges, hybridizations, and the structural environments are equivalent), then differences in electronegativity correlate well with differences in acid and base strength: The more electronegative atom shares its electrons less well, and so it is a poorer electron pair donor (weaker base) and its bond to a proton is more polar and easily broken (stronger acid). The same atom can appear in many different organic structures and, as long as the general description of the atom is the same (charge, hybridization, etc.), the pK_a values of those compounds are clustered together.

In the first row of Figure 0324, the central atoms are all closed shell, uncharged, sp^3, and have comparable structural environments. The identity of the atom, and the effect of the increasing electronegativity difference as you move from carbon to fluorine, correlate well with the observed pK_a values. In the second row, a few structurally diverse alcohols are shown along with their pK_a values. Compared with the vast range of values in the first row, all of these pKa values in the second row are more or less the same, and about the same as water. Uncharged, sp^3 hydroxyl groups in comparable structural environments of saturated hydrocarbon groups have pK_a values in the 16–19 range and are within 1–3 pK_a units of water. All of these molecules define the anticipated acid strength of an uncharged, sp^3 hydroxyl group.

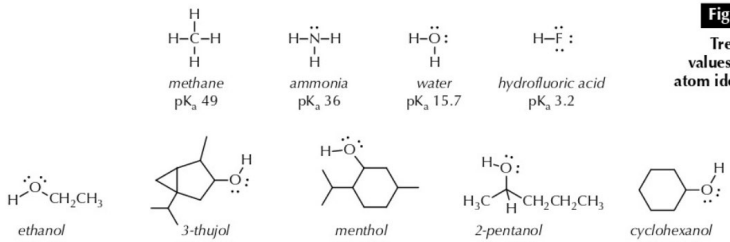

Figure 0324
Trend in pK_a values based on atom identity in a row.

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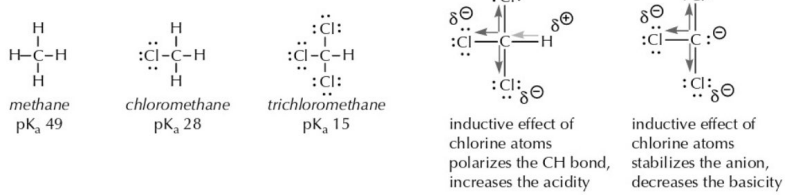
Electronegative atoms that are not directly attached to a hydrogen atom can also exert an influence on its acidity. Another effect of an atom's electronegativity is that it can be transmitted through bonds over a distance. Methane, as seen in Figure 0324, is exceptionally weak Brønsted acid (pK_a 49). Chlorine atoms, and the halogen atoms in general, can exert their electronegativity effect through more than one bond. In the short series of molecules shown in Figure 0325, as the number of chlorine atoms attached to the carbon increases, the pK_a of the CH bond decreases. This transmission of the bond polarity through many bonds is called the "inductive effect" of the halogen atoms (i.e., the halogen nuclei are inducing, or influencing, the slight reorganization of the electron density in the nearby bonds and making the CH bond more polar; see the fourth image in Figure 0325). Alternatively, one can think about the electronegative halogen atoms making the carbon more electron-poor than in methane, so the formation of a negative charge at the carbon (after deprotonation) is more relatively stabilized (fifth image in Figure 0325).

Figure 0325

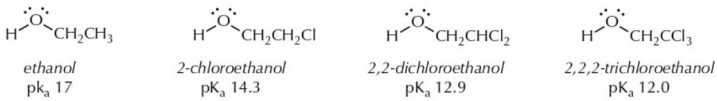
Inductive effect of electronegative atoms on nearby CH bonds (and on the conjugate base).


methane
pKa 49
chloromethane
pKa 28
trichloromethane
pKa 15
inductive effect of chlorine atoms polarizes the CH bond, increases the acidity
inductive effect of chlorine atoms stabilizes the anion, decreases the basicity

The inductive effect of nearby electronegative atoms is not restricted to CH bonds but is observed generally for any Brønsted acids and bases. Note the effect on the pK_a of the hydroxyl group, increasing the acidity of the OH bond by increasing the number of chlorine atoms four bonds away (Figure 0326).

Figure 0326

Effect of electronegative atoms on nearby OH bonds.



Charge: A positively charged compound is easier to deprotonate than its uncharged counterpart, and both are more easily deprotonated than the negatively charged version. The acidity of cationic compounds is higher than the uncharged versions (lower pK_a), while an anionic compound is a stronger base, more easily protonated, than its uncharged counterpart.

Uncharged organic molecules are generally more stable than charged ones. Starting from a cationic molecule and getting an uncharged one is a favorable direction, while starting with an uncharged molecule to get an anion is comparably harder to do. In the first row of Figure 0327, the difference in pK_a values between hydronium ion and water, and between ammonium ion and ammonia, are both consistent with this generalization. As with the family of comparable alcohols in Figure 0324, earlier, the structurally similar compounds to the ammonium ion, containing a cationic nitrogen atom in a hydrocarbon framework, cluster around an internally comparable pK_a range, in this case about 8–11.

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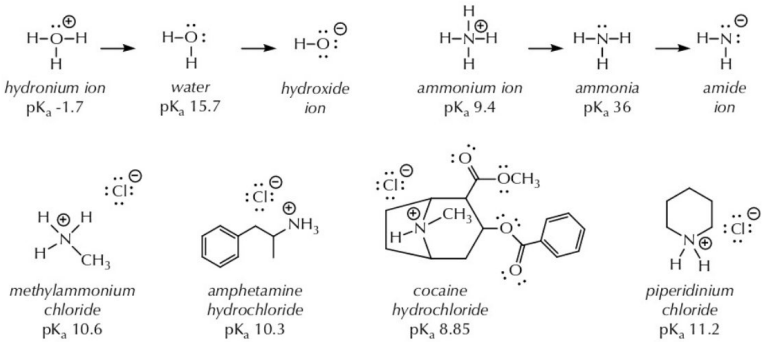
As in the earlier oxygen atom versus nitrogen atom examples, the basicity of the less electronegative sp^3 nitrogen atom in ammonia is higher than the more electronegative sp^3 oxygen atom in water. The stabilization of charge in their conjugate acids is a completely synonymous way to think about relative acidity: Protonation of the nitrogen in ammonia gives a more stable positive charge than protonation of the oxygen atom in water, also because a nitrogen atom is less electronegative than an oxygen atom. The resultingly more stable nitrogen cation is therefore less readily deprotonated (a weaker acid, pK_a 9.4) compared with the less stable oxygen cation (a stronger acid, pK_a -1.7).

Figure 0327

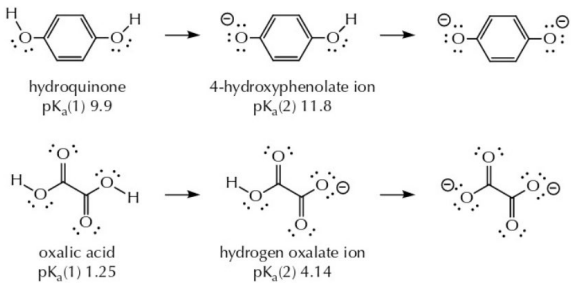
Trend in pK_a values based on change in charge (positively charged to uncharged).



Similarly, an already negatively charged anionic molecule is harder to deprotonate than its uncharged counterpart (Figure 0328). Although the two acidic protons in each of these examples, hydroquinone and oxalic acid, are identical in the fully protonated form, they have different pK_a values because, in experimental fact, the two deprotonation reactions cannot occur simultaneously, so the second deprotonation takes place from an anionic compound from which removing a proton is harder to do than from the uncharged version of the molecule.

Figure 0328

Trend in pK_a values based on change in charge (uncharged to negatively charged).



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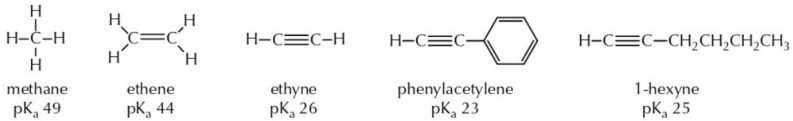
Hybridization: sp atoms are more electronegative than sp^2, that are in turn more electronegative than sp3 atoms. As the electronegativity of B in HB increases, the bond is more polar, and the acidity of the HB bond increases (pK_a decreases); the basicity of a more electronegative atom is less than a less electronegative atom as the electrons are less likely to be shared.

The difference in hybridizations is also a difference in electronegativity. Hydrogen atoms bonded to sp atoms have 50% s character, and the electrons are closer to the positive nucleus and more stable, having lower pK_a values than when they are bonded to sp^2 atoms. Both sp and sp^2 HB bonds are more acidic that those bonded to their sp^3 atom counterpart. And, as above, molecules can vary in structure but if the Brønsted acidic part of the molecule is retained, the pK_a values are about the same (Figure 0329).

Figure 0329

Trend in pK_a values based on differences in hybridization.



methane	ethene	ethyne	phenylacetylene	1-hexyne
pK_a 49	pK_a 44	pK_a 26	pK_a 23	pK_a 25

Atom size: Moving down a column in the periodic table, the HB bond is more acidic as the atom size difference increases.

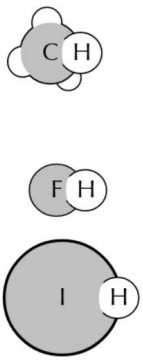
Electronegativity, which is the effective strength that the positive nucleus exerts on electrons, affects the size of atoms, and the relative magnitude of the effect of electronegativity on atom size differs in a row versus a column of elements in the periodic table.

In a row of the periodic table, the atomic radius of atoms gets only slightly smaller with increased electronegativity because second row electrons are all at the same energy level (Figure 0330). The effect of

Figure 0330

Competing effects of electronegativity and atom size difference on acid strength.

	pK_a value	bond dipole moment	bond length	bond strength (dissociation energy)
$H–CH_3$	49	0.4 D	1.094 Å	98 kcal/mol
$H–\ddot{N}H_2$	36	1.3 D	1.01 Å	104 kcal/mol
$H–\ddot{O}H$	15.7	1.5 D	0.96 Å	110 kcal/mol
$H–\ddot{F}:$	3.2	1.8 D	0.917 Å	136 kcal/mol
$H–\ddot{Cl}:$	-7	1.1 D	1.27 Å	103 kcal/mol
$H–\ddot{Br}:$	-9	0.83 D	1.41 Å	88.4 kcal/mol
$H–\ddot{I}:$	-10	0.38 D	1.61 Å	70.5 kcal/mol



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the large electronegativity differences in bond polarity dominates the observed properties (OH bonds are more acidic than NH bonds, all else being held equal).

In a column of the periodic table, however, the situation is different. Large changes in the atomic radius are observed as you move from period to period (row to row), in addition to the large differences in electronegativity. The electrons in the higher energy levels are less tightly held by the nucleus. At the top of a column, the HB bond would be predicted to be more acidic because of the greater difference in electronegativity, as seen in previous examples. This prediction is perfectly reasonable, but it does not account for the observed pK_a values, which are relatively more comparable for HB bonds in a column of the periodic table, and where acidity increases as you move down the column, towards the less electronegative atom. This observation does not mean that the predicted trend in acidity based on electronegativity is wrong, but rather that an additional factor is working in the opposite direction. This additional factor is proposed to be the significant weakening of the HB bond as the atom size difference between hydrogen and the other atom increases.

Reiterating those ideas with an example: Based upon the earlier generalizations about the effects of electronegativity on bond polarity, and acidity, it is reasonable to predict that HF would be a stronger Brønsted acid than HCl, and so on down that column. In fact, though, the experimental results for the pK_a values for HF through HI are (a) that they are relatively close in pK_a value compared with the differences seen in a row, and (b) that HI has the lower pK_a value, not HF (Figure 0330).

With the experimental facts about the pK_a values in hand, the explanation for this trend is built upon the atomic size difference as you move from period to period (up or down a column on the periodic table). Because covalent bonds are imagined as atoms sharing their valence electrons, the significantly larger iodine atom forms a longer and weaker bond with a hydrogen atom than a bromine atom (than chlorine, than a fluorine), and the orbitals being used for bonding are more mismatched in size and energy, and simply do not overlap (bond) as well.

While the intrinsic polarity of the bond, based on electronegativity difference, would predict HF as the stronger Brønsted acid, the intrinsic bond strength difference, with HF as the strongest bond, would predict HI as the stronger acid. Only the experimental results can tell us that the trend in atom size differences appear to be more significant than electronegativity differences. The fact that the pK_a values are so close to each other for this series is a testimony to the idea that both factors (size and polarity differences) are operating in competition, and that the size factor dominates slightly. If the observed trend in pKa values went in the other direction, a different generalization would have been created.

As in the previous comparisons, the pK_a values cluster when the variation in structure is only a difference in the hydrocarbon framework (Figure 0331). The pK_a values of the four molecules with uncharged, sp^3 OH bonds cluster in the 15–18 range, regardless of the hydrocarbon framework, while the four analogous molecules with uncharged, sp^3 SH bonds are all observed to have lower pK_a values than their OH counterparts, clustering in the 10–11 range.

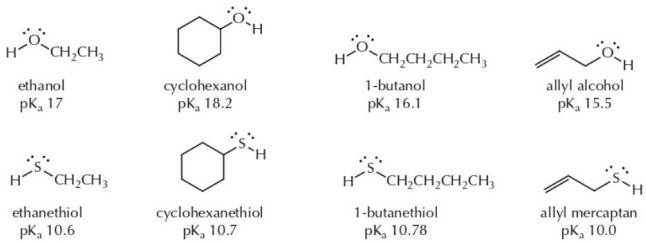

Figure 0331
Families of OH and SH Brønsted acids.

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Delocalization: With only a few noteworthy exceptions, such as constraints on molecular geometry, electron delocalization is a factor that leads to stabilization, and so it operates as an electronegativity effect: delocalized electrons are more stable than localized electrons, so the formation of a delocalized conjugate base corresponds to a stronger acid. Because delocalized electrons do not form a strong bond with a proton, the basicity of delocalized electrons is lower than localized electrons.

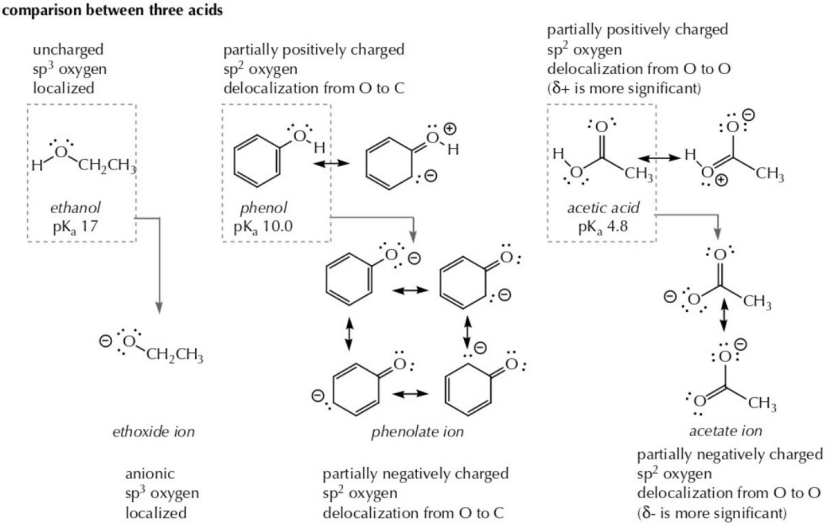
Resonance contributors are used to represent how we think electrons are distributed over multiple nuclei, providing better charge-charge interaction than in the localized electron option. There is no rule that says you should only look to the acid form (HB) to make comparisons of acid strength. You need to be particularly flexible in your perspective when delocalization is concerned: Sometimes it is clearer to look at the structure of the conjugate base to evaluate the strength of the acid. And because negative charges, positive charges, and open shell atoms can all be stabilized by delocalization, it is sometimes more convenient to look for the effect of delocalization on acid-base properties by comparing the acids. Often, you can look at both the acid and base strength comparisons and look for the correlation because, fortunately, the delocalization effect (stabilization) is consistent.

In Figure 0332, a series of OH bonds show a difference in their pK_a values. From the standpoint of the structure of the acids, the oxygen atom in ethanol in sp^3 (less electronegative) than the sp^2 oxygen atoms of phenol and acetic acid, so its pK_a is higher. Between phenol and acetic acid, the significance of the resonance contributor where there is a negative charge on an oxygen atom (acetic acid) is presumed to

Figure 0332

Effect of delocalization considered in both the acid and conjugate base structures.

comparison between three acids



comparison between three conjugate bases

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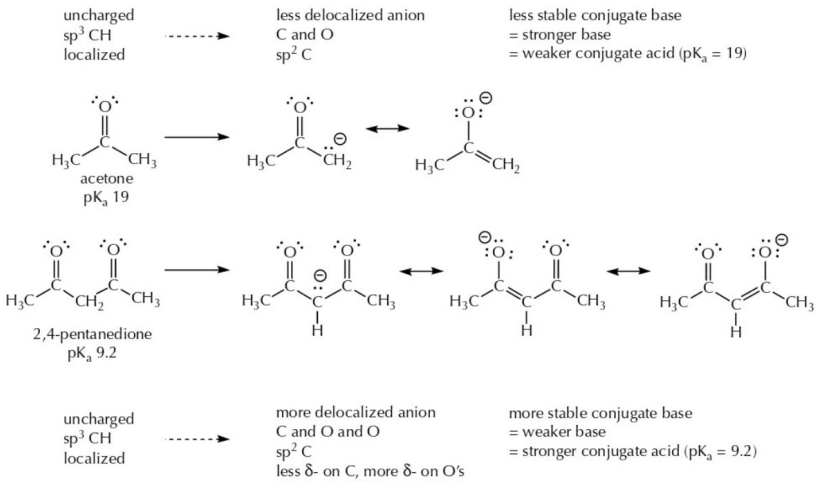
be greater than those in phenol, where the negative charge is on carbon atoms. And so the greater contribution of the positive charge on the oxygen atom of the OH in acetic acid is consistent with its lower pK_a value.

Alternatively, as shown in the lower part of Figure 0332, the stability of the anions formed in the conjugate bases can be compared. The anion of the acetate ion is more stable because of its more effective delocalization, and two equally significant resonance contributors, than in the case of phenolate ion, where the negative charge is on carbon atoms (even though there are more resonance contributors, the pK_a values tell us that they must not be as significant as those in acetate). The more stable anion, acetate, is the weaker base (least likely to share its electrons), and so its corresponding conjugate acid, acetic acid, is the stronger acid (most liked to be deprotonated, to result in the more stable anion). In contrast, ethoxide ion, with its localized sp^3 anion, is the most basic among these three examples and is derived from the weakest acid.

Sometimes the effect of delocalization cannot be deduced from the acid form. In the case of CH bonds, where the anion of the conjugate base can be delocalized (Figure 0333), the resonance contributors can only be drawn for the deprotonated form. The relative stability of the anions relates to their base strengths, and then by extrapolation to understanding the pK_a values of the original acids.

Figure 0333

Effect of delocalization considered in only the conjugate base structures.



Here are a few last general notes about pK_a.

Measurement. pK_a values can be measured in water itself for compounds whose values range from about -2 to 12. This range exists because experiments are limited by the acid-base strength of water. Measuring a pK_a value requires being able to observe experimentally meaningful amounts of both its acid form (HB) and its conjugate base form (B^-). Acids that are stronger than hydronium ion (pK_a -1.7), for instance, will

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be substantially deprotonated by the water molecules used as the solvent for making the measurement. To get pK_a values outside of this range of -2 to 12, the HB to B^- ratio is measured in a solvent other than water and a calculation is made to correlate with what it would have been in water.

Measurement records. The record-holder for the weakest acid is methane (CH4), with an estimated pKa value of 49–50. At that high level, you would expect enough methane would have the be dissolved at a high concentration in a beaker of water of a size to hold 8 planet earths before you might detect one (!) of the methane molecules becoming a proton donor. In other words, the conjugate base of methane is really strong. Only a few other dianion bases (e.g., O^{-2}, the conjugate base of hydroxide ion) have been observed to be slightly stronger than the conjugate base of methane.

The record holder for the strongest acid is HeH^+, the conjugate acid of helium gas, mentioned earlier in the context of there being no free protons in chemical solutions. The hypothetical pK_a value for HeH^+ is -63, making helium the poorest base on the planet. HeH^+ is so acidic that it can easily protonate oxygen (O_2) molecules. Said another way, HeH^+ (pK_a -63) is more acidic than sulfuric acid (pK_a -8) by about the same degree than sulfuric acid is more acidic than methane.

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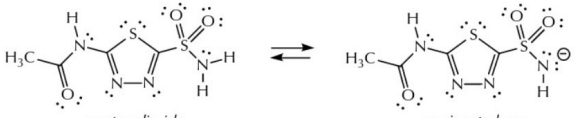
PRACTICE QUESTIONS

3.11 Acetazolimide is classified as an essential medicine by the World Health Organization (WHO). Introduced in 1952, it is used, among other things, for the treatment of glaucoma. The pK_a of acetazolimide is 7.4, and its acid and conjugate base forms are shown here.



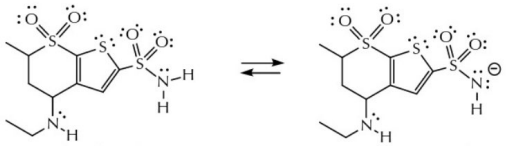
acetazolimide pK_a 7.4 *conjugate base of acetazolimide*

(a) What is the pH of a solution in which a 1:1 mixture of acetazolimide and its conjugate base are combined?

(b) If acetazolimide is placed into a solution of pH = 8.4, what will be the ratio of its acid to its conjugate base? [acid] : [conjugate base]

(c) What is the pH of a solution in which a 10:1 mixture of acetazolimide and its conjugate base are combined?

3.12 Dorzolamide is also used to treat glaucoma, and it was introduced in 1995 as an alternative to acetazolimide. Dorzolamide can be administered directly to the eye as a topical solution, whereas acetazolimide is administered orally, and so dorzolamide has fewer side effects. The pK_a of dorzolamide is 8.4, and its acid and conjugate base forms are shown here.



dorzolamide pK_a 8.4 *conjugate base of dorzolamide*

(a) What is the pH of a solution in which a 1:10 mixture of dorzolamide and its conjugate base are combined?

(b) If dorzolamide is placed into a solution of pH = 8.4, what will be the ratio of its acid to its conjugate base? [acid] : [conjugate base]

(c) What is the pH of a solution in which a 100:1 mixture of dorzolamide and its conjugate base are combined?

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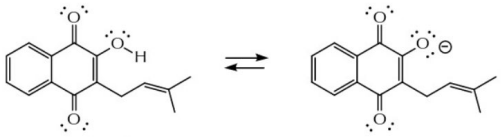
3.13 Lapachol, discovered in 1998, exhibits molluscicidal activity (*Struct Chem*, **1998**, *9*, 47) against mollusks that cause some tropical diseases. Its pK_a value was determined in 2008 to better study its biomedical effects.



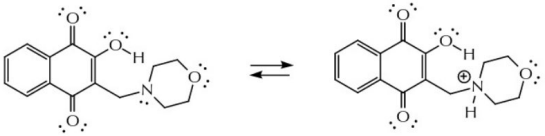
lapachol *conjugate base of lapachol*

(a) The pH of a 10:1 solution of lapachol and its conjugate base is 5.15. What is the pK_a of lapachol?

(b) Based on part (a), if lapachol is placed into a solution of pH = 9.15, what will be the ratio of its acid to its conjugate base? [acid] : [conjugate base]

(c) Based on part (a), what is the pH of a solution in which a 1:1 mixture of lapachol and its conjugate base are combined?

3.14 A synthetic morpholine derivative of lapachol was prepared in the 2008 study (see question 3.13) and tested, and it was not biologically active against mollusks. The pK_a of its conjugate acid was determined to be 8.60.



morpholine derivative of lapachol *conjugate acid of morpholine derivative of lapachol* (pK_a 8.60)

(a) What is the pH of a solution in which a 1:10 mixture of the morpholine derivative and its conjugate acid are combined?

(b) If the morpholine derivative is placed into a solution of pH = 9.60, what will be its ratio with respect to its conjugate acid? [acid] : [conjugate base]

(c) What is the pH of a solution in which a 1:100 mixture of the morpholine derivative and its conjugate acid are combined?

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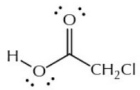
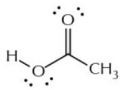
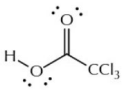
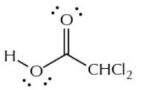
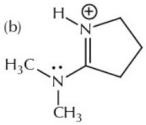
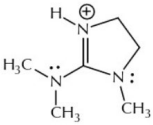
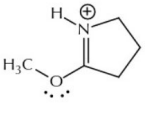
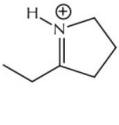
3.15 In each of the following questions, the series of molecules can be ranked from the most acidic [#1, lowest pK_a] to the least acidic [#4, highest pK_a] by using fundamental principles. Predict the ranked order. In the open space on the right, draw the structure of the conjugate base derived from the most acidic member in the series.

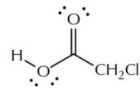
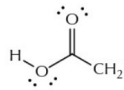
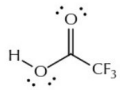
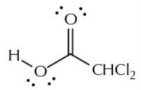
(a)

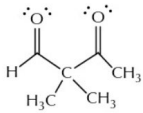
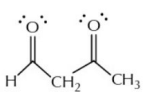
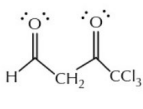
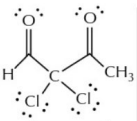
(b)

(c)

(d)

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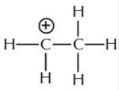

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3.4 Evaluating Brønsted Acid-Base Reactions

A. Predicting the Brønsted Acidity (pK_a Values) for Unfamiliar Compounds

As exemplified in the previous section (see Figures 0324, 0327, 0329, and 0331), families of structurally comparable Brønsted acids have their pK_a values clustered closely together. Consequently, a pK_a table of representative compounds can be used to make reasonable predictions about the pK_a values for molecules that are structurally analogous to the entry in the table.

To construct the best analogy between an unknown molecule and its counterpart in a pK_a table, the core structural features around the functional group should match as much as possible. Those features are (a) atom identity, (b) charge, (c) hybridization, (d) atomic size, and (e) the degree to which the acid and/or base forms share the same type of delocalizability. The identity of the functional group, any nearby functional groups, and the bonding framework of the local structural environment can all make a difference, too, in which your experience with making these analogies, more than anything else, comes into play.

The exact numerical pK_a value for an unknown compound cannot be predicted reliably; the actual pK_a value can only be determined by experiment. But by using representative pK_a values, we can make an informed estimate. This ability is a common practice in organic chemistry. In Figure 0334, a series of molecules with known (experimental) pK_a values is shown. An inventory of the structural features (characteristics) of the molecule is provided, followed by the structure of the molecule that best matches those characteristics from the pK_a table.

The agreement in Figure 0334 is good. All of the model compounds are within 1–2 pK_a unit of the experimental value, which is more than good enough for an estimate and would allow you to differentiate or rank the relative acidities. Some of the differences might have been anticipated. For instance, using trichloroacetic acid (the sixth entry in the figure) as the model for trifluoroacetic acid was the best choice, but you could have qualified the estimate a bit. Fluorine is more electronegative than chlorine, and so the inductive (electron-withdrawing) effect of the three fluorine atoms should be greater than that of the three chlorine atoms, and according to fundamental principles, the pK_a of trifluoroacetic acid would be predicted to be lower than that of trichloroacetic acid. And it is. Again, you would have no basis for estimating how much lower, numerically, but the trend within that pair is easy to predict.

Any purely predictive model that is meant to cover millions (and millions) of examples is never going to be perfect, however. The pK_a estimates for some molecules can end up being rather different than the observed values. These differences cannot be anticipated without significant experience; but seeing these cases can help you see how new structural effects are catalogued over time.

For example, if you needed to estimate the pK_a values for the most acidic sites in two structural isomers, salicylic acid and 4-hydroxybenzoic acid (Figure 0335), you might anticipate that the two pairs of values for these isomers would be close to one another. And there are two quite comparable structural analogies to use from the pK_a table, and you would use them for both estimates. Experimentally, though, the comparable functional groups in the two compounds differ by 3–4 pK_a units. In salicylic acid, the most acidic proton (the carboxylic acid) is stronger than its counterpart in 4-hydroxybenzoic acid, while the next most acidic proton (the phenolic OH) is weaker.

An experienced chemist automatically looks to any difference in the structure to explain differences in reactivity. Here, the obvious difference in the proximity of the two functional groups in salicylic acid would lead one to the question: can I see a defensible reason why the proximity of the two functional groups would have an effect on the pK_a values?

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Figure 0334

Predicting the Brønsted acidity using analogies from the pK_a table.

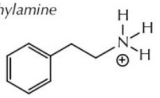
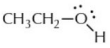
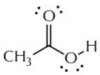
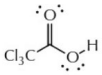
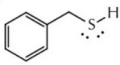
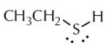
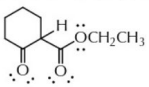
compound	characteristics	pK_a table analogy	pK_a experimental
β-phenethylamine 	N atom sp^3 hybridized cationic 3 Hs & 1 R group no deloc in acid or base	pK_a estimate (table): 10.6	pK_a experimental: 9.83
2,2-dimethyl-1-propanol	O atom sp^3 hybridized uncharged 1 H & 1 R group no deloc in acid or base	pK_a estimate (table): 17 	pK_a experimental: 14.82
isobutyric acid	O atom sp^2 hybridized uncharged 1 H & C=O with an R group deloc in acid and base	pK_a estimate (table): 4.8 	pK_a experimental: 4.86
quinoline	N atom sp^2 hybridized cationic 1 H & N atom in double bond deloc in acid	pK_a estimate (table): 5.2	pK_a experimental: 4.85
1-aminonapthalene	N atom sp^3 hybridized cationic 3 H & N atom on a double bond deloc in base	pK_a estimate (table): 4.6	pK_a experimental: 3.92
trifluoroacetic acid	O atom sp^2 hybridized uncharged 1 H & C=O with an CX_3 group deloc in acid and base	pK_a estimate (table): 0.64 	pK_a experimental: 0.23
benzyl mercaptan 	S atom sp^3 hybridized uncharged 1 H & 1 R group no deloc in acid or base	pK_a estimate (table): 10.5 	pK_a experimental: 9.43
ethyl cyclohexanone-2-carboxylate 	C atom sp^3 hybridized uncharged 1 H & 2 C=O with R & OR groups deloc in base	pK_a estimate (table): 9.2	pK_a experimental: 10.96

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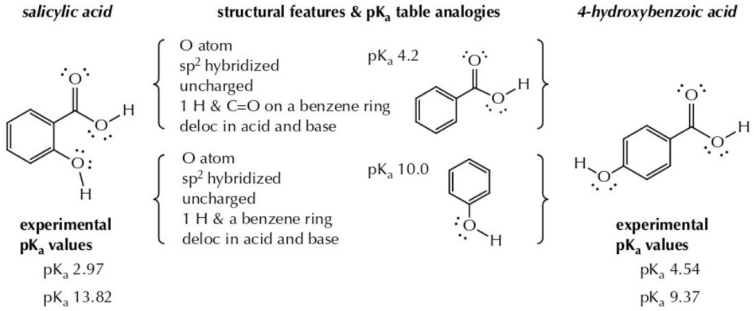
Figure 0335

Comparison of pK_a values in structural isomers: salicyclic acid and 4-hydroxybenzoic acid.

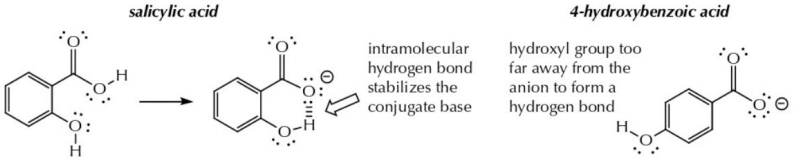


As shown in Figure 0336, when the first deprotonation takes place, the nearby phenolic OH group salicylic acid can participate in an intramolecular hydrogen bond with the anion of the conjugate base, while the OH group in 4-hydroxybenzoic acid is too far away, geometrically locking into position on the other side of the ring, and unable to reach the anion to provide the same interaction. The hydrogen bonding is a stabilizing effect and increasing the stability of the conjugate base in salicylic acid (weaker base) means that the acid form is more acidic (lower pK_a value). And in 4-hydroxybenzoic acid, the pK_a value of the carboxylic acid (4.54) is much like the model compound (4.2), while that of the salicylic is lower (2.97), and consistent with this explanation.

At this point, you might have been able to come up with a reasonable explanation with a few reminders about hydrogen bonding and the need to look at the conjugate bases. The more experience you get with more examples, the more likely it will be that you will think of factors such as hydrogen bonding whenever you see two functional group that are close enough to one another in a structure to have an interaction.

Figure 0336

The first deprotonation reactions of salicylic and 4-hydroxybenzoic acids.


salicylic acid
4-hydroxybenzoic acid
intramolecular hydrogen bond stabilizes the conjugate base
hydroxyl group too far away from the anion to form a hydrogen bond

The second deprotonation of these molecules forms a dianion, and so the deprotonation should be harder to do (higher pK_a) than in the model compound, which has a pK_a value of 10.0 (Figure 0335).

The second deprotonation of salicylic acid is indeed more difficult than expected based on the model (pK_a 13.82 versus 10.0), while the second deprotonation of 4-hydroxybenzoic acid is observed to be a little easier than the model compound (pK_a, 9.37 versus 10.0). An explanation for the differences in the second deprotonation reactions involves multiple structural features (Figure 0337).

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In the second deprotonation of salicylic acid, at least three factors might be included in the pK_a estimation in addition to forming a dianion: (1) the OH is being stabilized by a hydrogen bond, so it might be harder to deprotonate (higher pK_a); (2) deprotonation of the OH delocalizes the resulting anion into the other functional group, providing stabilization for the conjugate base (lower pK_a); and (3) deprotonation creates a pair of anions that are always in proximity because of fixed bonding positions, and repulsion of like charges is destabilizing for the conjugate base (higher pK_a).

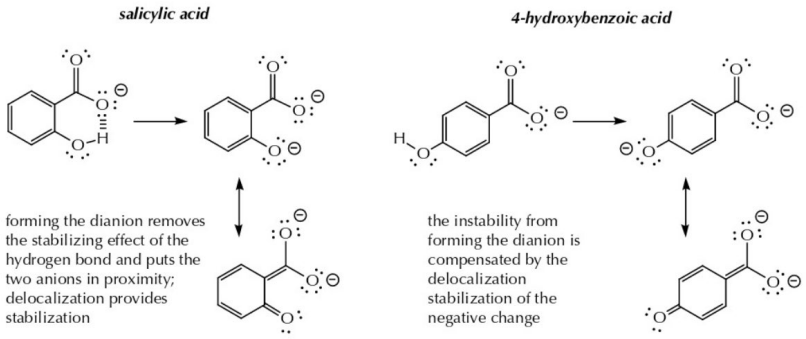
In the second deprotonation of 4-hydroxybenzoic acid, which also forms a dianion, there was no hydrogen bonding to overcome, and the two anions are not proximate, leaving only the other factor: Deprotonation of the OH delocalizes the resulting anion into the other functional group, providing stabilization for the conjugate base (lower pK_a). The single additional factor cited for 4-hydroxybenzoic acid is consistent with the experimental observation and guides the explanation. There is more significant delocalization in 4-hydroxybenzoic acid than in the model compound, and in the balance, the stabilization of the conjugate base by delocalization, lowering the pK_a value relative to the model compound, overcomes the formation of the dianion, which would raise the pK_a value relative to the model compound.

In salicylic acid, as in 4-hydroxybenzoic acid, the only resolution must derive from explaining the experimental result because there is no way to evaluate the balance of these factors. Forming the dianion, loss of the hydrogen bond, and creating proximate negative charges are all destabilizing effects for the conjugate base and would raise the pK_a value relative to the model compound, while the delocalization, as in 4-hydroxybenzoic acid, would lower the pK_a value relative to the model compound. Balancing factors is not a counting contest, so while the factors that tend to raise the pK_a value outnumber the ones that lower it by 3:1, it is not enough to make a reliable prediction. In this case, those three factors that raise the pK_a value appear to be overwhelming delocalization, because the pK_a value for the second deprotonation of salicylic acid is observed to be 13.82, almost 4 pK_a units or 104 times less acidic than the model compound, phenol, whose pK_a value is 10.0.

These two examples relied on hydrogen bonding as an additional factor. Other factors, such as the identity of the solvent and the identity of the counter ion, can influence the pK_a. The value obtained from any measurement depends on the experimental conditions used, and the more information you have about experiments, the better off you are to understand any observed differences.

Figure 0337

The second deprotonation reactions of salicylic and 4-hydroxybenzoic acids.


salicylic acid
4-hydroxybenzoic acid
forming the dianion removes the stabilizing effect of the hydrogen bond and puts the two anions in proximity; delocalization provides stabilization
the instability from forming the dianion is compensated by the delocalization stabilization of the negative change

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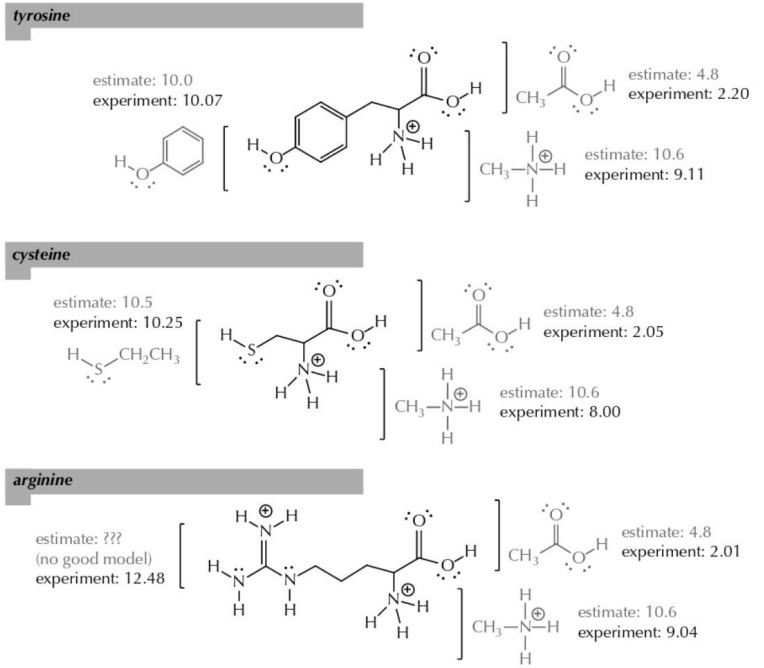
We return now to the three amino acids from Figure 0315, each of which contained three acidic protons in functional groups that varied in their structural features. Each of the groups can be considered separately, and a series of predictions follows. The actual pK_a values for these molecules are known, so you can see the comparisons (Figure 0338). One driving question from these data is "why are the carboxylic acids in amino acids (pK_a 2.01–2.20) about 1,000 times more acidic than in the carboxylic acid model compound (pK_a 4.8)?"

Figure 0338

The Brønsted acidity for amino acids using analogies from the pKa table: why are these acids more acidic than expected?



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In these three cases, the pK_a value of the most acidic proton is lower than anticipated. Two explanations for this difference can be constructed, which is common: one from the perspective of the acid form and one from the perspective of the conjugate base, as shown at the bottom of Figure 0338. Sometimes one of these perspectives is better, sometimes the other, and sometimes they both provide a useful look at what might be going on, which is what happens in this case.

Using the model compound in the pK_a table (acetic acid) as a guide for the acid form, the positively charged nitrogen is having an inductive electron-withdrawing effect comparable to placing multiple halogen atoms at the position next to the carbon-oxygen double bond (acetic acid, CH_3CO_2H, pK_a 4,8; versus trichloroacetic acid, CCl_3CO_2H, pK_a 0.64). Alternatively, looking at the deprotonated form, the proximity of the negative charge from the conjugate base to the positively charged nitrogen atom, plus the possibility of an intramolecular hydrogen bond, provides two forms of stabilization for the anion.

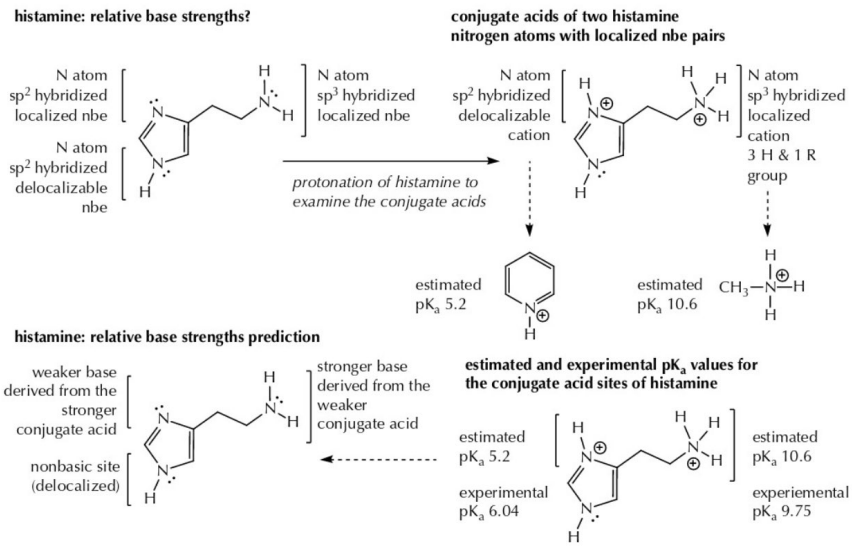
There is no need to select between these explanations, as all of these effects are certainly operating and cannot be isolated from one another. The purpose of the explanations is to understand as well as possible why the pK_a of the acids in amino acids are almost 1,000 times more acidic than in the model compounds, and both perspectives are consistent with the proximity of the electron-withdrawing and stabilizing effect of the positively charged nitrogen.

B. Using pK_a Values for Assessing Base Strength

Because the strength of an acidic is inversely related to the strength of its conjugate base, a pK_a table is equally a ranking of base strengths as it is acid strengths and creating a separate table and scale of base strengths is unnecessary. Histamine is a molecule with three potential Brønsted basic sites in it (Figure 0339).

Figure 0339

Assessing the relative base strengths of the atoms in histamine via their conjugate acids.


histamine: relative base strengths?
N atom sp² hybridized localized nbe
N atom sp² hybridized delocalizable nbe
N atom sp³ hybridized localized nbe
protonation of histamine to examine the conjugate acids
conjugate acids of two histamine nitrogen atoms with localized nbe pairs
N atom sp² hybridized delocalizable cation
N atom sp³ hybridized localized cation
3 H & 1 R group
estimated pK_a 5.2
estimated pK_a 10.6
histamine: relative base strengths prediction
weaker base derived from the stronger conjugate acid
nonbasic site (delocalized)
stronger base derived from the weaker conjugate acid
estimated and experimental pK_a values for the conjugate acid sites of histamine
estimated pK_a 5.2
experimental pK_a 6.04
estimated pK_a 10.6
experiemental pK_a 9.75

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To assess relative base strength, you need to consider the relative acid strengths of the conjugate acids. A weaker conjugate acid corresponds to a stronger base, and vice versa. By using the pK_a table to evaluate the relative acid strengths of the conjugate acids, the relative base strengths can be predicted or explained.

Two of the sites in histamine (see previous page) have localized nbe pairs, while the third is delocalized. We imagine delocalized electrons as being spread out over many nuclei, resulting in the associated stability. The delocalized electrons are more stable and less reactive towards forming new bonds, particularly towards forming the localized sigma bonds associated with acting as a base in a protonation reaction.

In the histamine example, the delocalized electrons do not have a good model compound in the pK_a table because they are not good bases. In predicting the difference in base strength between the two nitrogen atoms with localized electron pairs, then the structural characteristics of their conjugate acids can be analyzed exactly as in the examples from the preceding section. The two conjugate acids are cationic nitrogen atoms that differ according to their hybridization. Using the best model compounds from the pK_a table as comparisons, the estimated pK_a values are within 1 pK_a unit from the actual, experimental values.

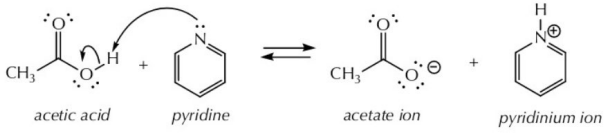
C. Predicting and Evaluating Brønsted Acid-Base Reactions (and Revisiting Hydrogen Bonding)

Brønsted acid-base reactions are a competition between two bases for a proton. Although the outcome from some acid-base reactions can be predicted by an analysis using general principles (Section 3.2D), using the representative examples in a pK_a table can extend this ability considerably, by making good analogies, to examples that would be impossible to do otherwise. The pK_a values also provide a way to make a quantitative estimate of how far to the right or left the acid-base reaction proceeds (the equilibrium constant, which is always defined by the way the chemical reaction has been drawn unless otherwise specified).

The standard method to evaluate the position of an acid-base reaction, as shown in the first example (Figure 0340), is to compare the relative strengths of the two acids, the one on the left-hand side (reactants) of the equation with the one on the right-hand side (products), which is the conjugate acid of the original base. The direction of the reaction favors the side of the weaker acid (higher pK_a value) because it represents the bonding between the stronger base with a proton.

Figure 0340

The Brønsted acid-base reaction between acetic acid and pyridine.



Acetic acid and pyridine are compounds that can be found on the pK_a table in this text. The outcome from the most likely Brønsted acid-base reaction can be drawn. Simply predicting the direction of the reaction is nearly impossible because there are so many structural differences between the two acids (although, admittedly, the name "acetic acid" gives a good clue). Acetic acid, on the left, possesses an uncharged sp^2 oxygen atom attached to a C=O and anticipates delocalization in both the acid and base forms. Pyridinium ion, the acid on the right, is the conjugate acid of pyridine. Pyridinium ion includes a cationic sp^2 nitrogen atom, which is part of a double bond, with delocalization of the positive charge. The comparison of effects from these structural features are not clear-cut for deciding how to rank the two acids: The more electronegative oxygen atom experiences more significant delocalization, but it is uncharged; the less electronegative nitrogen atom is cationic, and its delocalization is less significant because the resonance contributors that move the charge off of the nitrogen atom have open shell atoms.

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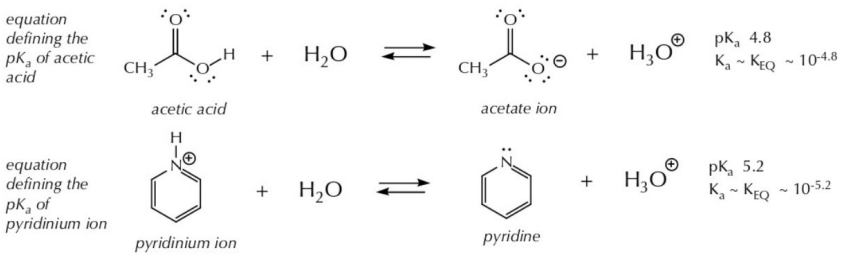
The pK_a values for both acetic acid and pyridinium ion are defined by the reaction of these two acids with water, and this means that the equations can be manipulated as a formal proof for the direct competition between the two acids. This proof does not need to be carried out every time, but seeing this relationship provides important scientific evidence for making a direct comparison of the pK_a values between the acid on the reactant side (on the left) and the acid on the product side (on the right).

In chemistry, equations with comparable terms can be manipulated, particularly by adding and subtracting terms, to establish new relationships derived from the original equations (Figure 0341).

Figure 0341

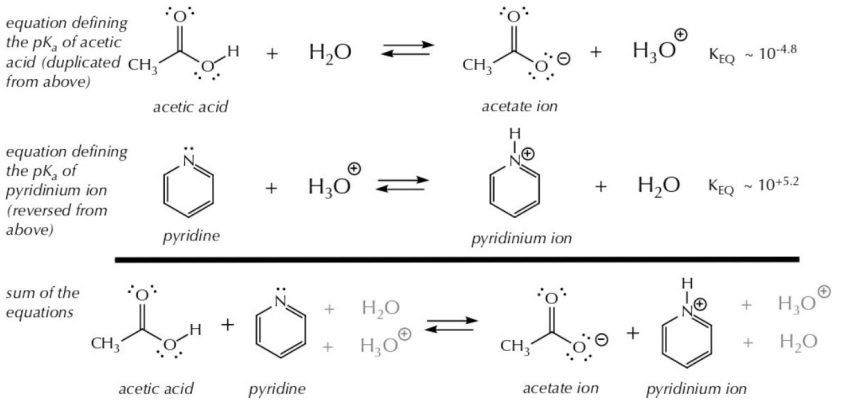
The underlying reason why different pK_a values can be used together in the same analysis.

i. the defining reactions for the pK_a values of acetic acid and pyridinium ion



Acetic acid has a lower pK_a than pyridinium ion (4.8 < 5.2), and its defining K_{EQ} with water is larger than that of pyridinium ($K_{EQ} \sim 10^{-4.8} > \sim 10^{-5.2}$). Acetic acid is the stronger acid.

ii. the reverse reaction between pyridine and hydronium ion has a high equilibrium constant



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In the lower portion of Figure 0341 (see previous page), the two chemical equations can be added, and the duplicated water and hydronium ion terms eliminated, leaving the original acid base equation between acetic acid and pyridine.

The combination of the two equilibrium constants is accomplished by combining the exponents ($10^{+5.2-4.8} = 10^{0.4}$), giving $10^{0.4}$, which is a value greater than 1.

This quantitative result is exactly what you expect from the qualitative result: acetic acid (pK_a 4.8) is a stronger acid than pyridinium ion (pK_a 5.2), so the competition between them should lie to the right, $K_{EQ} > 1$, on the side of the weaker acid.

The take-away result from this proof is a general principle: A reaction favors the formation of the weaker acid, which means that you can:

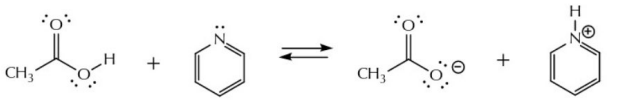
(a) compare the pK_a values to assess the direction of the equilibrium [K_{EQ} <1, =1, or >1], and

(b) use the pK_a values to estimate the value of the equilibrium constant.

The exponent (x) for the equilibrium constant 10^x is the difference between the pKa values [x = pK_a (product) – pK_a (reactant)]. The two assessments, (a) [<1, =1, >1] and (b) 10^x, need to make internally consistent mathematical sense, that is, if $K_{EQ} > 1$, then x in 10x is > 0, and if $K_{EQ} < 1$ (a fraction), then x in 10^x is <0 (Figure 0342).

Figure 0342

The Brønsted acid-base reaction between acetic acid and pyridine favors the products.



pK_a 4.8 (a) pKa 5.2 (weaker) > pKa 4.8 (stronger), $K_{EQ} > 1$
(b) estimated $K_{EQ} = 10^{[5.2-4.8]} = 10^{0.4}$ (which is >1) pK_a 5.2

Note that the estimated K_{EQ} in this example is only slightly over 1 (100.4 = 2.5), meaning that the competing criteria between the oxygen and nitrogen atoms of the two acids are nearly equivalent.

A K_{EQ} of 2.5 means that there will be 2.5 times more pyridinium ions than acetic acid, which means that about 30% of unreacted acetic acid would remain, at equilibrium, if acetic acid and pyridine were mixed in a 1:1 ratio. The general principles about any equilibrium reaction apply here, and the ratio of starting materials to products can be affected by changing the experimental conditions. For example, the absolute amount of a given product can be increased by increasing the proportion of one of the starting materials, or by removing one of the products (for example, by precipitation or its going to the gas phase). In this reaction, using a large excess of pyridine relative to the amount of acetic acid would necessarily shift the reaction towards the products side, consuming the acetic acid in the process, as the concentrations adjust to achieve the overall equilibrium ratio (Le Châtelier's Principle).

Combining (a) the predictive model of reactions using pK_a values, with (b) the technique of estimating the acid-base strengths for unknown compounds, means that outcomes from many unfamiliar reactions can be predicted. As the difference in pK_a values between the two competing acids gets larger, the reactions can be considered more and more complete, that is, as an equilibrium that lies so far to one side as to have effectively none of the starting materials present (or that none of the possible products form,

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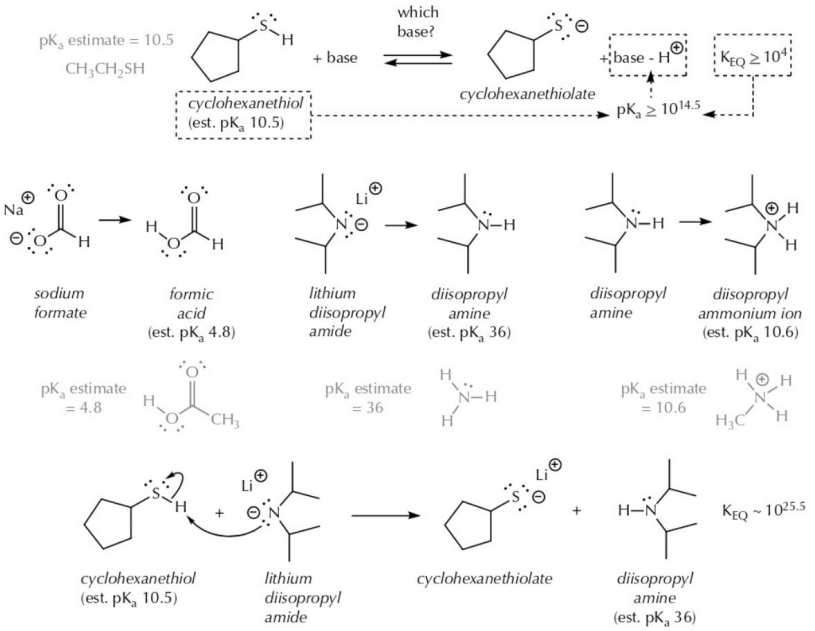
in the case where an extremely weak acid-base pair were combined). For two acids with a pK_a difference of 3 units, the equilibrium ratio would be 1,000: 1 (10^3), while a difference of 7 pK_a units would represent a 10,000,000: 1 ratio (10^7). At some point, the amount of the minor component is so undetectably small that the proton transfer can be considered to lie completely on one side of the reaction.

There is no consensus for what ratio is considered to be a "completely" protonated or deprotonated reaction product. In this text, rather than set a single arbitrary value for what is considered to be a complete proton transfer reaction, we will simply specify a K_{EQ} value (the threshold value), as needed, as a part of a discussion or in instructions. For example, you might want to know whether a reaction, as written, has estimated K_{EQ} of $> 10^5$. As a K_{EQ} value greater than 1, the weaker acid would need to be on the product side. To get this estimated value, and recalling that pK_a values are exponents, the pK_a of the weaker acid, on the products side of the equation, would need to be at least 5 pK_a units higher than the stronger acid, serving as a starting material.

It is common, in an experimental laboratory setting, to have to decide which base to use for carrying out a deprotonation reaction of a given acid. This decision can be made using the process described above. The question might be "Which of the following three bases (sodium formate, lithium diisopropylamide, and/or diisopropylamine) should I use to deprotonate cyclopentanethiol with a $K_{EQ} > 10^4$?" (Figure 0343). The question defines the bases, and so cyclopentanethiol is the acid. While none of these exact molecules are in the pK_a table, good estimates of the acid and base strengths can be made, by analogy.

Figure 0343

Cyclopentanethiol plus sodium formate, lithium diisopropylamide, and diisopropylamine.



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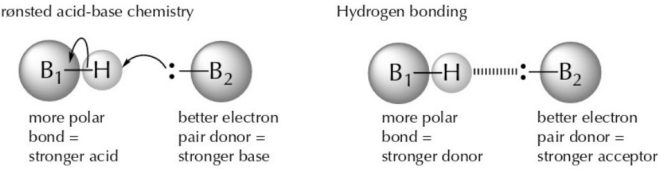
Another way to pose the original question more directly might be to ask "How do you characterize a base that can deprotonate cyclopentanethiol with a $K_{EQ} > 10^4$?" The estimated pK_a value of cyclopentanethiol is 10.5. If it needs to be deprotonated with a $K_{EQ} \geq 10^4$, then the acid-base reaction (a) needs to lie on the right ($K_{EQ} > 1$), and (b) the conjugate acid on the products side needs to have a pK_a value greater than or equal to 14.5 to get an estimated $K_{EQ} \geq 10^4$ [i.e., 10^x ; $x \geq 4$, according to product pK_a ($\geq$ 14.5) – reactant pK_a (10.5)]. The pK_a values for the conjugate acids of these three bases needs to be estimated by analogy, also. The best analogy for the conjugate acid of sodium formate is acetic acid, with a pK_a equal to 4.8; for lithium diisopropylamide, the analogy is ammonia, pK_a = 36; and for diisopropylamine it is methylamine, pK_a =10.6. Only lithium diisopropylamide has a conjugate acid with a pKa $\geq$ 14.5, so the conclusion is that only lithium diisopropylamide would satisfy the conditions of the question.

Another topic that can be addressed by comparing pK_a values is hydrogen bonding and predicting the relative strengths of individual hydrogen bonds. Hydrogen bonding shares all of the features of Brønsted acid-base chemistry, except that we do not talk about the transfer of the proton, only the force of attraction for the hydrogen bond acceptor (an electron pair donor) for a hydrogen bond donor (a polar sigma bond involving a hydrogen atom). In principle, Brønsted base strength should correlate with being a good hydrogen bond acceptor, and Brønsted acid strength with being a good hydrogen bond donor (Figure 0344).

Figure 0344

The relationship between Brønsted acid-base strength and hydrogen bonding.



Not every acid-base pair is expected to give a hydrogen bond. The combination of a strong acid with a strong base simply results in the Brønsted acid-base proton transfer reaction, while a too weak acid-base pair means the combination of a poor hydrogen bond donor with a poor hydrogen bond acceptor.

As might be predicted, the strongest hydrogen bonds are observed when the pK_a difference between the hydrogen bond donor (an acid) and the conjugate acid of the hydrogen bond acceptor (a base) approaches zero, and the proton transfer is not overtly favored in one direction or the other.

On the large magnitude end of the ΔpK_a range (strong acid/strong base, i.e., a reaction that forms a weak conjugate acid), the proton transfer takes place (or it has already taken place), and there is no hydrogen bonding.

But as the ΔpK_a approaches zero, the competition between the base (hydrogen bond acceptor) and the conjugate base (associated with the hydrogen bond donor) becomes a tie, and the proton is more readily shared between them (Figure 0345).

D. The Relationship Between pH and the Composition of a Solution

So far in this section, three quantitative aspects of using pK_a values in organic chemistry have been introduced: (a) predicting pK_a values for unknown compounds, (b) predicting the outcome of an acid-base reaction, and (c) estimating of the magnitude of the position of an acid-base reaction. The last topic looks at the relationship between the concentration of an acid (HB), its conjugate base (B^-), and the pH of the solution in which the acid is dissolved. To do this, we return to the Henderson-Hasselbalch equation.

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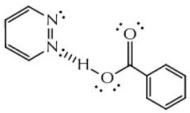
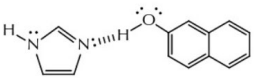
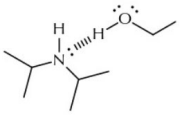
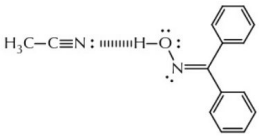
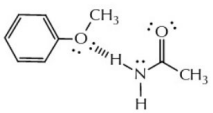
Figure 0345

As ΔpK_a approaches zero, the strength of hydrogen bonding increases.

structures and pK_a values	distance and energy data	ΔpK_a and qualitative strength
 pyridiazine (conjugate acid pK_a 2.5) benzoic acid pK_a 4.2	N--H-O distance: 2.50-2.55 Å H-bond energy 12-15 kcal/mol	ΔpK_a = 1.7 very strong
 imidazole (conjugate acid pK_a 7.0) 2-napthol pK_a 9.51	N--H-O distance: 2.55-2.65 Å H-bond energy 7-12 kcal/mol	ΔpK_a = 2.51 strong
 diisopropylamine (conjugate acid pK_a 11.05) ethanol pK_a 17	N--H-O distance: 2.65-2.75 Å H-bond energy 4-7 kcal/mol	ΔpK_a = 5.95 medium
 acetonitrile (conjugate acid pK_a -10.1) benzophenone oxime pK_a 11.3	N--H-O distance: 2.75-2.85 Å H-bond energy 2.5-4 kcal/mol	ΔpK_a = 21.4 weak
 anisole (conjugate acid pK_a -6.5) acetamide pK_a 15.1	O--H-N distance: 2.85-3.0 Å H-bond energy 1-2.5 kcal/mol	ΔpK_a = 31.6 very weak

Based on data reported in: *Accounts of Chemical Research*, **2009**, *42*, 33.

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In Section 3.3C, the Henderson-Hasselbalch equation is derived, and it is the defining equation for the pK_a to pH relationship, for a Brønsted acid (HB): $pK_a = pH - \log([B^-]/[HB])$, which comes from the defining reaction of HB with water: $HB + H_2O \rightarrow H_3O^+ + B^-$ (Figure 0346).

Figure 0346

The defining reaction and the defining equation for pK_a.

Defining reaction for acidity of HB

$$H_2O + H\text{-}B \rightleftharpoons H_3O^{\oplus} + B^{\ominus}$$

Henderson-Hasselbalch Equation

$$pK_a = pH - \log\left(\frac{[B^-]}{[HB]}\right)$$

constant

Effect 1: vary $[B^-]/[HB]$, monitor pH

(a) $[B^-]:[HB] = 1:1$

conjugate base and acid in equal concentration; no change in pH

$$pK_a = pH - \log\left(\frac{1}{1}\right)$$

$$pK_a = pH - 0$$

$$pH = pK_a$$

(b) $[B^-]:[HB] = 10:1$

more conjugate base than acid; pH shifts to more basic

$$pK_a = pH - \log\left(\frac{10}{1}\right)$$

$$pK_a = pH - (+1)$$

pH increases by 1 unit because pK_a is a constant

Effect 2: vary pH, monitor $[B^-]/[HB]$

(a) pH +2 over pK_a

increasing pH = shift towards increasing base concentration

$$pK_a = [pH + 2] - \log\left(\frac{[B^-]}{[HB]}\right)$$

$$pK_a = [pH + 2] - \log\left(\frac{100}{1}\right)$$

$$pK_a = [pH + 2] - (+2)$$

$[B^-]:[HB] = 100:1$ because pK_a is a constant

(b) pH -4 under pK_a

decreasing pH = shift towards increasing acid concentration

$$pK_a = [pH - 4] - \log\left(\frac{[B^-]}{[HB]}\right)$$

$$pK_a = [pH - 4] - \log\left(\frac{1}{10{,}000}\right)$$

$$pK_a = [pH - 4] - (-4)$$

$[B^-]:[HB] = 1:10{,}000$ because pK_a is a constant

Because the pK_a value is a constant, pH and the $[B^-]/[HB]$ ratio are linked. There are two experimentally observable effects suggested by this linkage.

Effect 1: If you vary the $[B^-]/[HB]$ ratio, then the pH of the solution will change, accordingly.

Recall how the first of these experiments gives a convenient way to measure a pK_a value. If the $[B^-]/[HB]$ ratio is set to 1, using a 50:50 mixture of $[B^-]:[HB]$, then $pK_a = pH$, and the pH measurement yields the pK_a value.

Effect 2: If you vary the pH of the solution, the $[B^-]/[HB]$ ratio will change, accordingly.

The Henderson-Hasselbalch equation also conveys how the acid-base $[HB]:[B^-]$ ratio changes if the substance is put into solutions of fixed pH values (called buffer solutions). Buffers are solutions where the pH is maintained by mixing fixed amounts of weak acids and their conjugate bases (e.g., sodium bicarbonate, $NaHCO_3$, with sodium carbonate, Na_2CO_3). Adding small amounts of other acids or bases only inconsequently perturbs the solution equilibrium and the pH remains constant.

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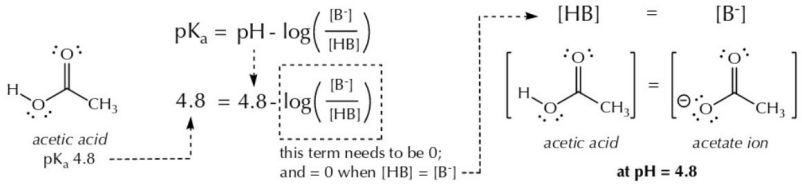
For instance, if acetic acid (pK_a 4.8) is placed into a buffer solution of pH 4.8, the [HB]:[B⁻] ratio of the acetic acid to acetate (conjugate base) will be 1:1.

According to the equation, if the pH of the solution is equal to the pK_a value of HB, then the only way for $pK_a = pH - \log([B^-]/[HB])$ to be mathematically true is if the log term is zero. In a pH 4.8 buffer solution, the concentration of the acid form, acetic acid, is equal to its conjugate base form, acetate ion (Figure 0347).

Figure 0347

The ratio of [HB]:[B⁻] is 1:1 when the pH of the solution equals the pK_a value of HB.



If the pH of the buffer is lower than the pK_a value (a movement in the acidic direction), then there is an increase in the concentration of hydronium ion (H_3O^+), which shifts the defining reaction towards the side of the starting materials ([HB] > [B⁻]). On the other hand, if the pH of the buffer is higher than the pK_a value (a movement in the basic direction), then there is a decrease in the concentration of H_3O^+, which shifts the defining reaction towards the products ([B⁻] > [HB]) (Figure 0348).

Figure 0348

The effect of changing the pH on the position of the defining pK_a reaction.

$$H_2O + HB \rightleftharpoons H_3O^{\oplus} + B^{\ominus}$$

$$K_{EQ} = \frac{[H_3O^{\oplus}][B^{\ominus}]}{[H_2O][HB]}$$

What happens to the [HB]:[B⁻] ratio if the pH decreases?

1. starting point: HB in solution at equilibrium
2. decrease the pH of the solution (increase $[H_3O^+]$)
3. the equilbrium shifts towards the left:
   increasing the concentration of HB
   decreasing the concentration of B⁻

In summary: < pH, then [HB] > [B⁻]

What happens to the [HB]:[B⁻] ratio if the pH increases?

1. starting point: HB in solution at equilibrium
2. increase the pH of the solution (decrease $[H_3O^+]$)
3. the equilbrium shifts towards the right:
   decreasing the concentration of HB
   increasing the concentration of B⁻

In summary: > pH, then [B⁻] > [HB]

Quantitatively, according to the defining equation, every change in the pH of the buffer solution by 1 unit causes the [HB] to [B⁻] ratio to change by a power of 10 (Figure 0349).

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Figure 0349

The quantitative effect of changing the pH on the ratio of HB to B^-.

$$pK_a = pH - \log\left(\frac{[B^-]}{[HB]}\right)$$

	$pH = pK_a + 2$	$[HB] : [B^-] = 1 : 100$	**condition #2** increase pH above pK_a to increasingly basic conditions $[B^-] > [HB]$ by powers of 10 for each ΔpH of +1
	$pH = pK_a + 1$	$[HB] : [B^-] = 1 : 10$	
condition #1 reference point $pH = pK_a$ $[HB] = [B^-]$	$pH = pK_a$	$[HB] : [B^-] = 1 : 1$	
	$pH = pK_a - 1$	$[HB] : [B^-] = 10 : 1$	**condition #3** decrease pH below pK_a to increasingly acidic conditions $[HB] > [B^-]$ by powers of 10 for each ΔpH of -1
	$pH = pK_a - 2$	$[HB] : [B^-] = 100 : 1$	

The experiment outlined in this figure is another restatement of Effect #2, above, derived from the mathematics of the Henderson-Hasselbalch equation: If you vary the pH of the solution in which HB is placed, the HB:B^- ratio will adjust, accordingly, because the pK_a value is a constant.

Condition 1 in Figure 0349 is the reference point. When the pH of the solution is the same as the pK_a value, then the HB:B^- ratio is 1:1 (as also detailed for acetic acid in Figure 0347).

When you raise the pH of the solution (Condition 2) above the pK_a value (increasing basicity), the HB:B^- ratio goes up by powers of ten favoring the concentration of the conjugate base, that is, $[HB]<[B^-]$. Because pK_a and pH values are exponents, each change of 1 unit represents a 10-fold increase in the ratio.

When you lower the pH of the solution (Condition 3) below the pK_a value (increasing acidity), the HB:B^- ratio goes up by powers of ten favoring the concentration of the acid, that is $[HB]>[B^-]$.

By knowing the pK_a value for a Brønsted acid, you can predict the $[HB]:[B^-]$ ratio in solution at any specified pH value, particularly whether $[HB] < [B^-]$, $[HB] = [B^-]$, or $[HB] > [B^-]$. And by the difference in concentration based on the ratio, the degree to which an acid is described as being its acid form versus in its deprotonated (conjugate base) form is being specified.

If "complete protonation" was defined as being a 10,000:1 (104:1) ratio, then by putting the compound into a solution that was at least 4 pH units below its pK_a value (i.e., on the acidic side) would be needed to achieve that ratio (or greater).

Returning to acetic acid (pK_a 4.8), for example. The composition of acetic acid (HB) to acetate (B^-) in a buffer solution of pH 4.0, which is on the acidic side of the pK_a value, will have a higher concentration of the original acid form (acetic acid) compared with its conjugate base (acetate ion); $[HB]>[B^-]$. When the ΔpH value is an integer away from the pK_a value, then the power-of-ten ratios shown in Figure 0349 apply, and the $[HB]:[B^-]$ ratio is 10^x, according (Figure 0350).

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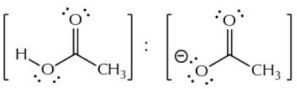
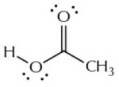
Figure 0350

The composition of acetic acid to its conjugate base, acetate ion, at various pH values.

$$pK_a = pH - \log\left(\frac{[B^-]}{[HB]}\right)$$





acetic acid
pK_a 4.8

pH = 9.8	1	:	100,000	pH ≥ 8.8 if the "completely deprotonated" threshold is defined as ($K_{EQ} \geq 10^4$)
pH = 8.8	1	:	10,000	
pH = 7.8	1	:	1000	
pH = 6.8	1	:	100	
pH = 4.8	1	:	1	
pH = 3.8	10	:	1	
pH = 1.8	1000	:	1	
pH = 0.8	10000	:	1	pH ≤ 0.8 if the "completely protonated" threshold is defined as ($K_{EQ} \leq 10^{-4}$)
pH = -0.2	10000	:	1	

In a solution whose pH matches the pK_a value of 4.8, the ratio of acetic acid to acetate ion is 1:1, while a solution whose pH is higher than 4.8 will favor a higher concentration of acetate ion over acetic acid.

If an [HB]:[B⁻] ratio of 10^4 was selected for acetic acid to be considered as in its "completely protonated" (acidic form, [HB]:[B⁻] = 10^4:1) or "completely deprotonated" (basic form, [HB]:[B⁻] = 1:10^4), then that would establish the threshold pH values above and below, which we would say that only the basic or acidic forms would be present, as noted in Figure 0350. Again, the 10^4 ratio is a value that needs to be defined in context, and could have been selected as 10^3, 10^5, or 10^6, and so on. Or a question might have simply been asking what form of acetic acid was present as the major component of the solution at a given pH value. The principle for either determining the ratio or the pH does not change, so keep an eye out for the ratio to be defined as part of the question, or the pH.

For more complex molecules with multiple acidic sites, each of the acidic sites can be considered separately.

When the different pK_a values are close to each other, it becomes more difficult to give an exact numerical value to the composition in solution, but the major form can be predicted with confidence (Figure 0351).

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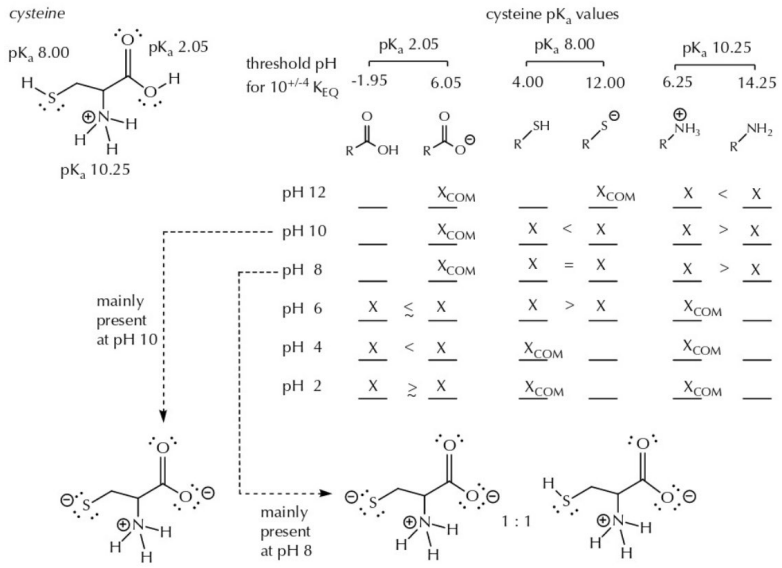
Figure 0351

The composition of cysteine in solution at various pH values.



In the amino acid cysteine, shown previously (Figure 0338), there are three Brønsted acidic sites in the molecule. The experimentally determined pK_a values are known and shown in Figure 0351. In the simplest version of the analysis for what form of the molecule is in solution, the three acidic sites can be analyzed separately from each other, and the question reduces to whether the acid or conjugate base form of each group is expected to be the major form anticipated to be present at a specified pH value.

For the purposes of this example, we will once again set the threshold value for analysis to be a 10^4 ratio, and we will define that these groups are "completely" protonated or deprotonated when the $[HB]:[B^-]$ ratio is $> 10^4$.

Looking at the figure, the pK_a value for the most acidic proton in cysteine is 2.05. Using a 10^4 ratio as the threshold ratio, the corresponding threshold pH values will be 2.05–4 = -1.95. At a pH at or below -1.95, we will consider this functional group to be in its fully protonated (HB) form.

Between pH -1.95 and 2.05, we are on the acidic side of the pK_a value, so both forms are present, but $[HB]>[B^-]$. At pH 2.05, $[HB]=[B^-]$. Above the pH = 2.05, on the basic side of the pK_a value, with $[B^-]>[HB]$ until we reach the second pH threshold (2.05+4 = 6.05), after which time we would say that the functional group is fully deprotonated and only in its $[B^-]$ form.

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The other two Brønsted acidic sites are treated the same way. For the site with the pK_a value of 8.00, the pH threshold for its being fully protonated (pH 8.00-4) is 4.00, and for being fully deprotonated (pH 8.00+4) is 12.00. The threshold range for the third site, $pK_a = 10.25$ is 6.25 to 14.25. Again: below 6.25, we would say that this functional group is in its fully protonated (HB) form. Between 6.25-10.25, both forms are present and [HB]>[B^-], and at 10.25, [HB]=[B-]. Between 10.25-14.25, both forms are present but [B^-]>[HB], and only the [B^-] form is expected above pH 14.25.

The grid of which forms are present relative to a given pH value is shown in the figure to keep track of the state of protonation for each of these groups. An "X" is used to tell whether that form will be present. An equality or inequality sign is used to indicate the relative relationship when both are present. And "X_{COM}" is used if the ratio of the forms is outside of the 10^4 value, and the group is to be considered completely in its protonated or deprotonated form.

The structural interpretation for what is expected in solution, as the major component(s), is included for the pH 10 and pH 8 cases.

Identifying the charge on a molecule according to the pH of a solution has practical significance. For example, in the biochemical research technique of electrophoresis, the separation of charged protein molecules in a gel depends in great part on the overall charge on the molecule, and that charge depends on the pH. Selecting a pH and thinking about the resulting charges in a complex molecule, as done here for cysteine, is a commonly applied practice.

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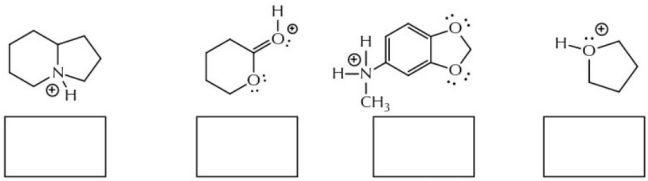
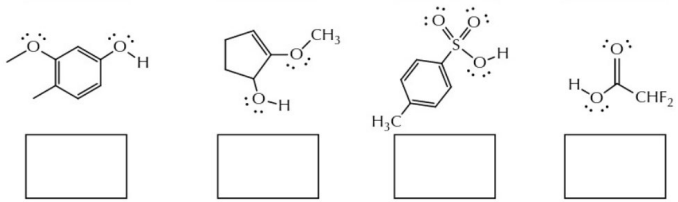
PRACTICE QUESTIONS

3.16 Estimate the pK_a values for the most acidic functional group in the following molecules based on structural analogies with the entries in the pK_a table.

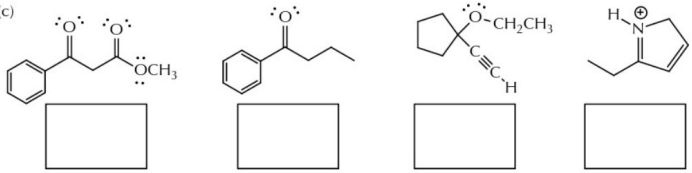
(a)



(b)

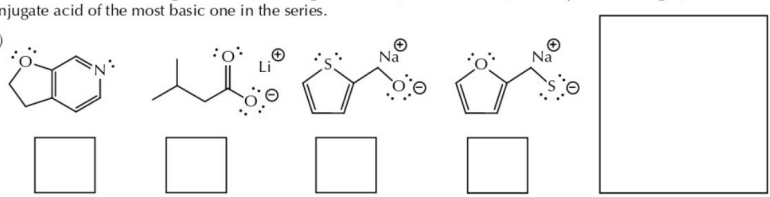


(c)

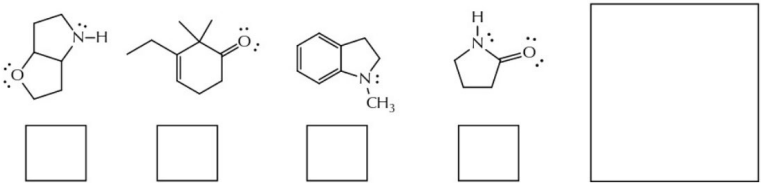


3.17 Rank the relative base strengths for the following molecules (1 = most basic). In the space at the right, draw the conjugate acid of the most basic one in the series.

(a)



(b)



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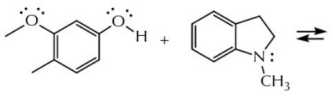
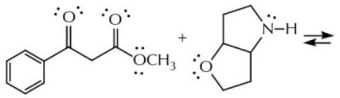
3.18 Predict and provide the curved arrow mechanism for the most likely Brønsted acid-base reaction between the following pairs of molecules. Use the pK_a table to create the most appropriate analogies for the pK_a values, and also estimate the magnitude of the equilibrium constant for each reaction.

(a)



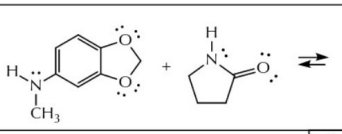
estimated equilibrium constant:

(b)



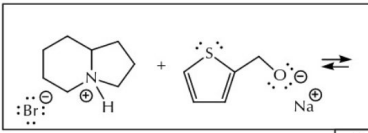
estimated equilibrium constant:

(c)



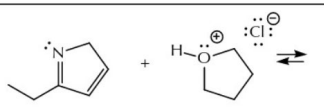
estimated equilibrium constant:

(d)



estimated equilibrium constant:

(e)



estimated equilibrium constant:

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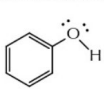
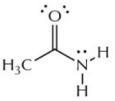
3.19 Each of the following molecules can be found on the pK_a table. For each one, predict what the composition will be in a buffer solution at the given pH value. Use a threshold value of $\geq 10^4$ for the ratio to be considered as completely protonated or deprotonated. If both the acid and base form are predicted to be present, draw them both and label them as major, minor, or equal. If only one form is expected, only draw it alone and not the other.

phenol  pyridine acetamide 

(a) pH 5			
(b) pH 10			
(c) pH 13			
(d) pH 5.5			
(e) pH 8			

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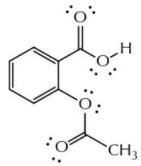
3.20 The experimentally determined pK_a values for the following molecules are provided. What is the structure of the major species in solution at the given pH value? In the case where there are two forms that are equally likely, provide both. Using a threshold equilibrium ratio for complete protonation or deprotonation of $\geq 10^3$, indicate if the major form is also the exclusive form.

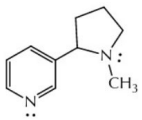
(a) *aspirin* (pK_a 3.4) at pH 5 and pH 7



pH 5

pH 7

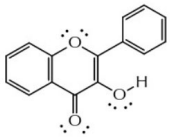
(b) *nicotine* (pK_as for the conjugate acids are 3.41 and 8.10; which is which and why?) at pH 8 and pH 5



pH 8

pH 5

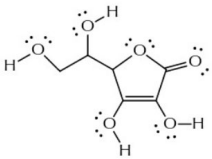
(c) *3-hydroxyflavone* (pK_a 8.68) at pH 5 and pH 10



pH 5

pH 10

(d) *vitamin C* (pK_a values are 5.0 and 11.3; which is which and why?) at pH 5 and pH 10



pH 5

pH 10

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Reflections About Science: Relative Measurement and Points of Reference

Three bowls of water (A, B, and C) are lined up on a table. Pierre Curie puts his hands into bowls A and B, while Marie Curie puts her hands into bowls B and C.

You ask Marie and Pierre to affirm that one of the bowls has warm water and the other is cool, and they both say yes. You ask Pierre "Which one is warm?" and he says, "Bowl B." And Marie immediately says, "*Non, Pierre*... bowl B is the cool one."

Can the same bowl of water be both warm and cool? Sure. Warm and cold, tall and short, fast and slow, long and short, strong and weak...all of these are comparative terms that have no absolute meaning without a point of reference. In this story, bowl A had ice-cooled water in it, bowl B had water at room temperature, and the water in bowl C had just been boiled.

A pK_a value is not absolute measurement; it is a relative measurement that uses water as a point of reference. If a different solvent were used, the acidity constant would have a different value. In fact, there are different acidity scales that are built upon different solvents, particularly using organic solvents rather than water.

The terms acid and base are also relatively defined. After all, substances such as water are amphoteric, a word that refers to having both acidic and basic properties. Water has a conjugate acid and it has a conjugate base. Even sodium hydroxide, by definition, is a potential Brønsted acid! After all, its conjugate base, sodium oxide (Na_2O) exists; it is a mineral used for making ceramics, and if you add water to sodium oxide you get the acid-base reaction that results in sodium hydroxide as the weaker acid relative to water.

And yet, we end up using terms such as "acid" and "base," "fast" and "slow," "tall" and "short" with an understanding about a common human point of reference. If you went into the lab to retrieve a solution of acid, you would not come back with sodium hydroxide. If you give directions and say "turn left at the tall building," you are assuming something about the average experience of your listener and the environment of the nearby buildings. A fast-moving airplane is certainly moving at a different pace than a fast-moving river, a fast-moving runner, or a fast-moving glacier.

In my "Reflection" essay at the end of Chapter 1, I discussed the important understanding that Heisenberg brought to science, namely, that "method and object can no longer be separated." What we measure depends on how we do the measurement, and how we design an experiment to make a measurement is a decision by humans, and that decision is defined and limited by our theories, our models, and our biases about the world.

Modern philosophers of science remind us that observations are theory-laden; that is, what you are able to see, and how you design an experiment, are guided by your perceptions and your past experiences. One of the reasons we embrace the idea of working with people who have different backgrounds and experiences is that they can collectively bring a much broader set of perceptions to any situation, and together, the group can see a broader array of options than people who only have a set of commonly shared experiences. After all, Marie, who has always lived in an arid, desert climate, has a wholly different perception of what "cold" means relative to Pierre, who has only lived in an arctic climate.

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Summary

Acid-base reactions are an ideal introduction to the principles of organic structure and reactivity. All of the variation introduced about organic structures comes into play, and the importance of working with experimental observations is critical to understanding reactivity.

Two ways of defining acids and bases are useful. According to the Lewis definition, an acid is an electron pair acceptor, and a base, an electron pair donor. Important Lewis acids, containing an open shell atom, include compounds such as boron trifluoride, BF_3, and aluminum chloride, $AlCl_3$. Such acids are also known as aprotic acids. According to the Brønsted-Lowry definition, an acid is a proton donor, and a base, a proton acceptor. A Brønsted acid is also known as a protic acid.

Atoms bearing nonbonding electron pairs, such as oxygen, nitrogen, and sulfur, are the basic sites in molecules or ions. Lewis bases and Brønsted bases are therefore the same: protic acids transfer a proton to such atoms, and Lewis acids coordinate with them.

The Brønsted acid-base reaction is a competition between bases for the more effective bonding to a proton. The loss of a proton converts a protic acid into its conjugate base. The basicity of a species depends on the position in the periodic table of the atom bearing the nonbonding electrons. Basicity decreases for a series of atoms that go from left to right across any period or down any group. An anion containing a given atom is always more basic than an uncharged molecule containing the same atom. Delocalized electrons are less basic than localized ones. The inductive effect of electronegative groups also stabilizes electron density and lowers basicity.

The acidities of protic acids are quantified as their pK_a values, which are derived from equilibrium constants in their acid-base reaction with water. Experimentally, the pK_a value is a pH measurement in which the acid whose acidity constant is being determined is mixed with an equimolar amount of its conjugate base. Relative base strength can also be assessed using x values through the conjugate acid-base relationship: A stronger base is associated with a weaker conjugate acid, and vice versa.

The position (direction) of an acid-base reaction can be assessed by a comparison of the relative acidities (pK_a values) of the acid and conjugate acid in a reaction. A reaction lies to the side of the weaker acid-base pair, and a quantitative estimate of the equilibrium constant can be made using the difference in pK_a values. The composite ratio of an acid with is conjugate base at a specific pH can be evaluated by a comparison with the pK_a value. At pH values below the pK_a, more of the acid form exists; at pH values above the pK_a, more of the base form exists.

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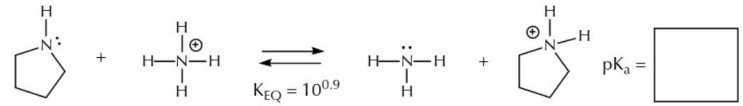
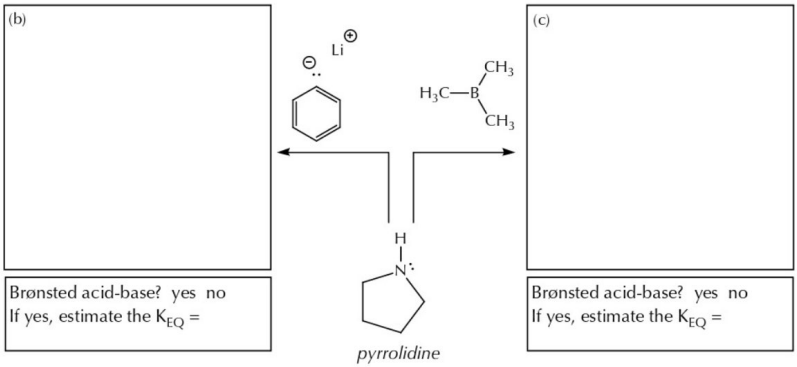
CHAPTER QUESTIONS

3.21 (a) Given the following experimental information, what is the pK_a of the pyrrolidinium ion?



pyrrolidine *pyrrolidinium ion*

Predicting the outcomes from chemical reactions is based on a combination of structural features, classifications (e.g., Lewis acid-base complexation, Brønsted acid-base), and experimental criteria (e.g., a pK_a table). Pyrrolidine, shown here in the center, reacts with each of the other compounds that are shown above the arrows. Provide the products. Complete structures and balanced equations must be shown; ionic substances should be clearly indicated as charge-separated ions. For Brønsted acid-base reactions, estimate the K_{EQ} for the reaction. You will need the pK_a you determined in part (a) for some of these examples.



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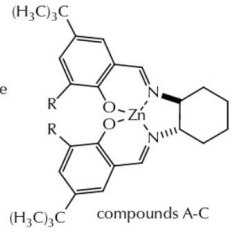
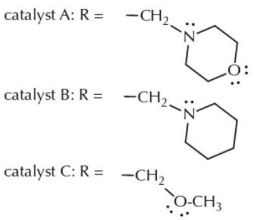
3.22 Chemists at the University of Pennsylvania designed a series of new catalysts (A, B, C) that differed by the basicity of the portion of the molecule located at the position labeled "R" in the structure shown to the right. They judged the relative basicity of these groups by examining the pK_a values of their conjugate acids.

(*Organic Letters*, **2001**, *3*, 3053)

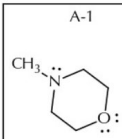
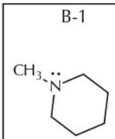
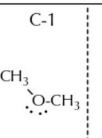


compounds A-C



The chemistry of the simpler molecules shown below (A-1, B-1, and C-1) can be studied as a way to understand the more complex ones, above.

(a) Draw the conjugate acids for A-1, B-1, and C-1. In any case where more than one conjugate acid is possible, draw the structure for the weaker (more stable) conjugate acid. Experimentally, the pK_a values for these three conjugate acids are -3, 6, and 8 (in no particular order). Place the pK_a value corresponding to each of the conjugate acids in the correct answer space (do not worry about drawing a counterion).

A-1	B-1	C-1
		
pK_a =	pK_a =	pK_a =

(b) Based on your answer to part (a), which of the molecules (A-1, B-1, or C -1) is most basic?

circle one:	briefly: how the pK_a guides this decision?
A-1 B-1 C-1	

(c) In a few sentences, give the structural basis for the difference in basicity that you predicted for molecules A-1 and B-1. Be sure your answer identifies which one is more basic and explains why this is so, using relevant structural information.

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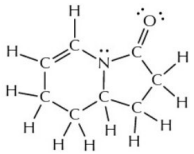
3.23 Compound M was used in a synthesis of an alkaloid found in the skin of neotropical poison-dart frogs.



compound M

(*Tetrahedron Letters*, **2001**, *42*, 6621)

(a) Protonation of molecules with nitrogen and oxygen heteroatoms, such as those found in compound M, often occurs on those atoms. In this case, would it be more favorable to protonate the nitrogen atom or the oxygen atom? In order to answer this: (i) draw the two protonation products, (ii) consider the relative stability of the two resulting ions, and (iii) decide which of these conjugate acids would have the lower pK_a value.

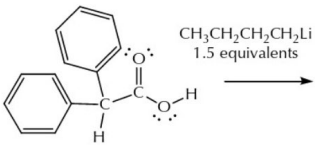
protonation at nitrogen	protonation at oxygen

(b) Which is these conjugate acids forms more readily?

circle one:	protonation at nitrogen	protonation at oxygen

(c) Provide a brief reason for your choice in part (b); use structural drawings and words.

3.24 Compound N has two relatively low pK_a values (4.5 and 13). If a 1.5: 1 ratio of the extremely strong base called butyllithium ($CH_3CH_2CH_2CH_2Li$) is combined with compound N, then a 50:50 ratio of two new molecules forms in addition to the conjugate acid of butyllithium (which is called butane, $CH_3CH_2CH_2CH_3$). Draw structural formulas for the two products of this reaction.



compound N

$CH_3CH_2CH_2CH_2Li$
1.5 equivalents

+

50:50 ratio of these two (plus butane: $CH_3CH_2CH_2CH_3$)

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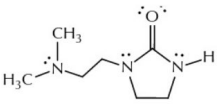
3.25 Many important biologically active molecules contain imidazolidin-2-one subunits. For example, compound A has been investigated as a potentially useful antidepressant. The pK_a of the most acidic proton in compound A is 17, whereas the conjugate acid formed by protonation of the most basic atom in compound A has a pK_a of 11.



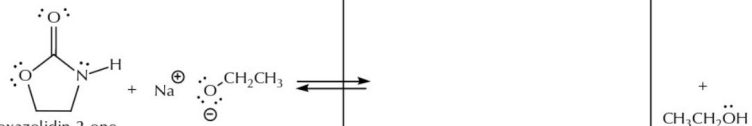
compound A $pK_a = 17$

pK_a of conjugate acid $= 11$

(a) Provide the structure of the major species present in a pH 9 solution of molecule A.

(b) Provide the structure of the compound formed ($K_{EQ} > 10^3$) when compound A is treated with 1 equivalent of HF.

(c) Oxazolidin-2-ones are structurally related to imidazolidin-2-ones, and are also of medicinal importance. Provide the equilibrium constant for the reaction between the simple oxazolidin-2-one (compound B) and sodium ethoxide. Your answer should be in the form $K_{EQ} = 10^x$ (fill in the box with the number that represents x). Also, draw the Lewis structure for the most significant resonance form of the conjugate base of the oxazolidin-2-one (compound B).

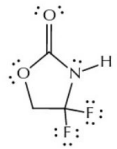


oxazolidin-2-one ($pK_a = 14$)
compound B

$K_{EQ} = 10^{\square}$

most significant resonance form of conjugate base of oxazolidin-2-one (B)

(d) Is compound C more acidic or less acidic than compound B? Briefly explain your answer.



compound C

circle one:	*brief explanation*
Compound C is *more acidic* *less acidic* than compound B.	

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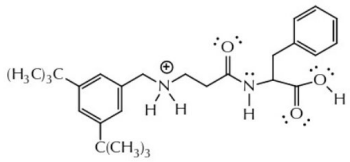
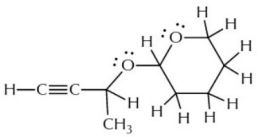
3.26 The following compound was prepared to study interesting molecular structures called rotaxanes (*J Org Chem*, **2003**, *68*, 2547). Draw the structure of the major form of the molecule that would be expected to exist in a buffer solution of pH = 6.

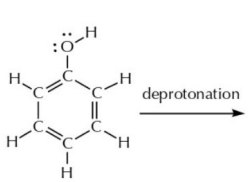


3.27 Which of the following bases could be used to completely mono-deprotonate the molecule shown below ($K_{EQ} > 10^3$)? Mark an "X" in the "yes, it can" or "no, it cannot" box, as appropriate.



	CH_3Li	$NaOCH_3$	KCl	$NaNH_2$	NH_3	LiSH
Yes, it can	☐	☐	☐	☐	☐	☐
No, it cannot	☐	☐	☐	☐	☐	☐

3.28 Deprotonation of the molecule drawn below gives a conjugate base that can be represented by a set of five resonance forms that all have closed shell atoms. Draw all five resonance forms. Place the most significant pair of contributors to the actual structure in the spaces indicated.



most significant contributor #1 | most significant contributor #2

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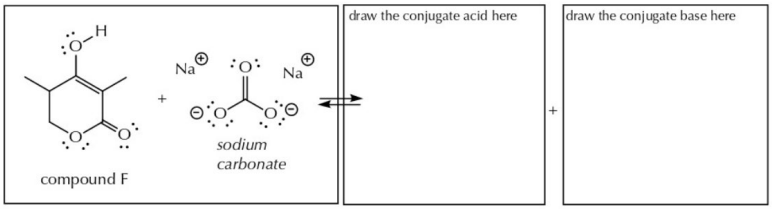
3.29 Complete the following according to the directions associated with each of the questions. All of the non-hydrogen atoms in these answers have octet (closed shell) electron configurations.

(a) Compound F has a pK_a value of 9.2. Provide (i) the curved arrow mechanism for the reaction between compound F and sodium carbonate; and (ii) the products of the reaction, using complete structures in a balanced equation.

(i) the curved arrow mechanism

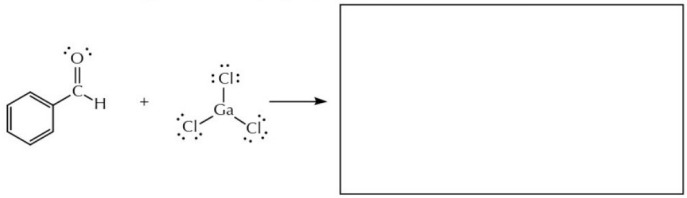
(ii) the products from the reaction (as indicated in the boxes) complete molecules, including counterions, should be shown



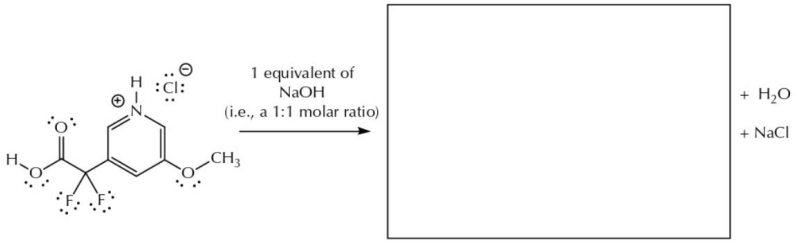
(b) What is the estimated value of the equilibrium constant for the reaction in part (a)?

K_{EQ} =

3.30 The element gallium (Ga) is located under aluminum, in the boron group, on the periodic table, and its chemistry is comparable to what you expect from boron. Thus, gallium halides such as $GaCl_3$ are commonly used as Lewis acids in organic reactions (*Org Lett*, **2018**, *20*, 4954). Draw the product from this reaction.



3.31 Draw the expected mono-deprotonation reaction product using one molar equivalent of sodium hydroxide.



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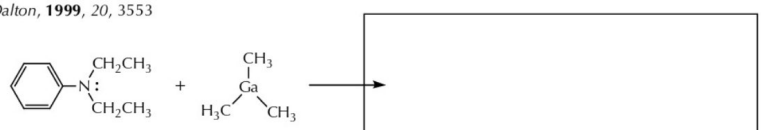
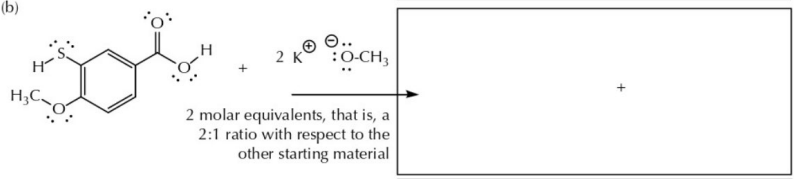
3.32 Complete the following chemical reactions as required by the question. Include nonbonding electron pairs and formal charges in any required drawings, and don't forget to account for all of the atoms!

(a) *Dalton*, **1999**, *20*, 3553

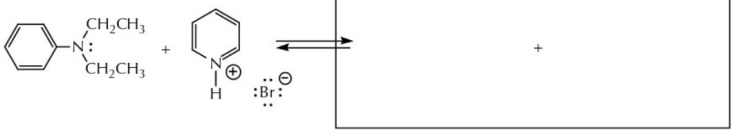


(b)



2 molar equivalents, that is, a 2:1 ratio with respect to the other starting material

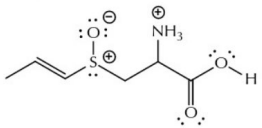
(c)



(d) In part (c), the experimental equilibrium constant (K_{EQ}) is measured to be $10^{1.4}$. Thus, the actual pK_a for the conjugate acid that you drew on the right, in that equation, must be what value?

3.33 The lachyrmatory factor in onions is what brings tears to your eyes. It is derived from compound D (*ACS Chem Bio*, **2017**, *12*, 2296). Compound D is observed to have pK_a values of 2.2 and 12.5. In a solution of pH = 10, what are the two structures in equilibrium, and which one is in the higher concentration?

compound D



highest concentration at pH = 10

second highest concentration at pH = 10

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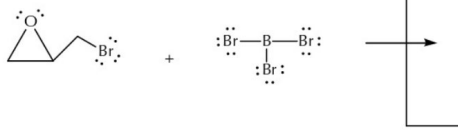
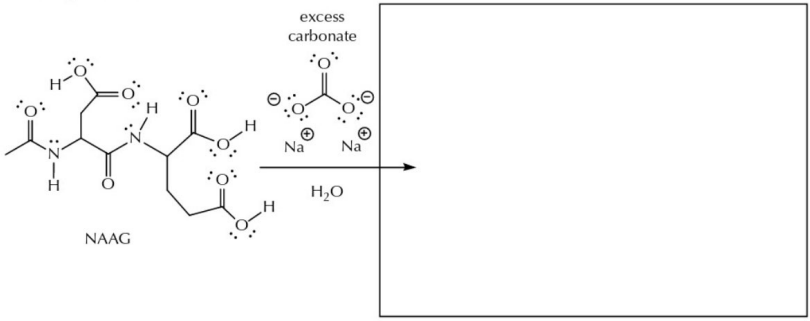
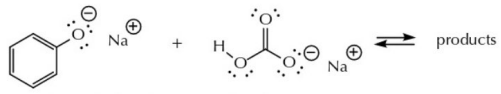
3.34 Recalling that ranking Lewis base strengths follows the same trends as ranking Brønsted base strength, predict the product from this highly selective Lewis acid-base complexation reaction.



3.35 What is the structure of the reaction product between NAAG (one of the most prevalent neurotransmitters in mammals) with excess aqueous sodium carbonate? Give the molecule, derived from NAAG, including any necessary counterions.



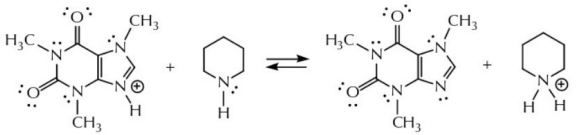
3.36 It is possible to use pK_a values to assess an equilibrium constant. Is the value of the equilibrium constant for the 1:1 reaction between conjugate base of phenol and sodium bicarbonate greater than, less than, or equal to 1?



conjugate base of phenol *bicarbonate*

K_{EQ} is (*circle one*):
greater than 1
less than 1
equal to 1

3.37 New pK_a values can be determined from measuring the equilibrium constant for an acid-base reaction that is carried out with a reaction partner whose pK_a value is known, and inferring what the pK_a value of the new compound must have been. Based on the following data, what is the estimated pK_a value for the conjugate acid of caffeine?



conjugate acid of caffeine

$K_{EQ} = 10^{-1.2}$

$pK_a = 9.3$

pKa value for the conjugate acid of caffeine:

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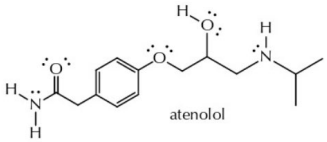
3.38 Atenolol is a drug introduced in 1976 to treat cardiovascular diseases, particularly hypertension. Its efficacy against mortality has been shown to be minimal, however, and there are some negative side effects, such as a risk of provoking diabetes type 2, so its use has been downgraded.



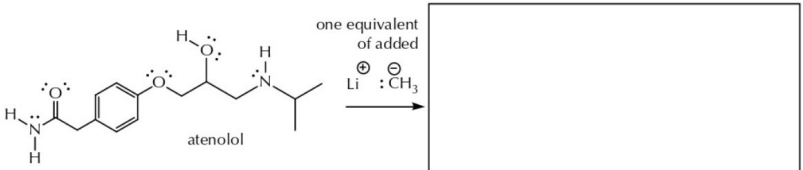
(a) How many delocalizable electron pairs are there in atenolol?

(b) The normal pH value of blood is 7.365. Draw the structures for the two forms of atenolol that exist at this pH value (place the major form in the right-hand space, and the minor form in the left; counterions, that is, spectator ions, do not need to be shown).

minor form of atenolol at pH 7.365

major form of atenolol at pH 7.365

(c) Methyllithium (CH_3Li) is a strong Brønsted base. Draw the expected major products when one stoichiometric equivalent of methyllithium is added to atenolol (that is, when they are combined in a 1:1 ratio). Be sure to provide the complete set of product structures that balances the chemical equation.

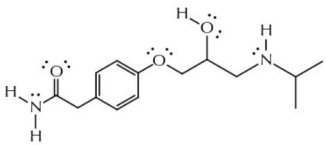


(d) Reminder: evaluating hydrogen bond strength mirrors closely the Bronsted acid-base properties.

Select the best hydrogen bond donor in atenolol and show its interaction with a water molecule.

Select the best hydrogen bond acceptor and show its interaction with a water molecule.

If there are equivalent groups in either case, you only need to indicate one of them.



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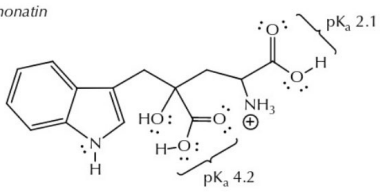
3.39 Monatin is a high intensity sweetener (*J Org Chem*, **2005**, *70*, 4569). The two carboxylic acids in monatin have pK_a values of approximately 4.2 and 2.1, respectively. Based on the structure of the molecule, shown below, propose an explanation for the 100-fold difference in acidity between these two carboxylic acid groups.

monatin

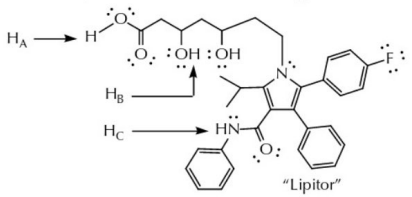


Relatively strong Bronsted bases (conjugate acid $pK_a > 16$) can deprotonate monatin. When 1.0 equivalent of base is added to monatin, its conjugate base forms. As more base is added, another deprotonation takes place. What is the structure of the conjugate base formed after the addition of 1.0 equivalent of base, and what is the structure after the second deprotonation occurs?

monatin plus 1.0 equivalent of base

monatin plus 2.0 equivalents of base

3.40 Atorvastatin (originally sold by Pfizer under the name "Lipitor") is a top selling pharmaceutical in the US. This compound, called a statin, is used for the treatment of high cholesterol levels.



Acid-base chemistry plays a big role in this drug's activity. For each of the bases shown below, decide which of the protons in Lipitor (H_A, H_B, and/or H_C) would be removed ($K_{EQ} \geq 10^3$) when an excess of the base is added to Lipitor.

	base	H_A	H_B	H_C
(a)	CH_3Li	☐	☐	☐
(b)	KCl	☐	☐	☐

	base	H_A	H_B	H_C
(c)	NH_3	☐	☐	☐
(d)	$NaSCH_3$	☐	☐	☐

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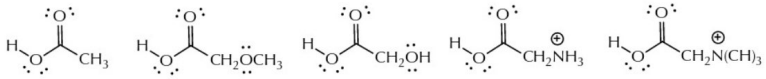
3.41 The pK_a values for a series of compounds that are structurally related to acetic acid are provided below.

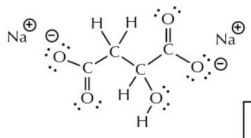
(a) Relative to unsubstituted acetic acid, two of the groups (OH and NH_3^+) can provide both inductive and hydrogen bond stabilization for their conjugate bases, while the other groups provide only inductive stabilization. Do the pK_a values support the conclusion that "having inductive and hydrogen bond stabilization in their conjugate bases is more stable than having only inductive stabilization"? What evidence supports your answer?



acetic acid pK_a 4.8 | *methoxyacetic acid* pK_a 3.54 | *glycolic acid* pK_a 3.83 | *glycine* pK_a 2.34 | *betaine* pK_a 1.84

answer & explanation

(b) The doubly deprotonated form of malic acid, named malate, is shown. In its fully protonated form, malic acid has two acidic protons, with pK_a values of 3.7 and 5.4. Draw the missing product of the following reaction, in which only one proton is delivered to malate by H_3O^+. Estimate the K_{EQ} (10^x) for the reaction and justify the product(s) you have predicted to form with words and structures.



malate

H_3O^+ (one equivalent)

$K_{EQ} \sim$

$+ H_2O + Na^+$

explanation for selectivity in the protonation reaction:

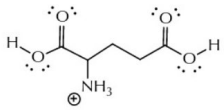
3.42 Glutamic acid is an amino acid having 3 acidic protons with pK_a values of 2.3, 4.1, and 9.2.

(i) In the first box, assign these pK_a values to the appropriate H in the structure of glutamic acid.

(ii) Monosodium glutamate is an additive in many food items, although it can cause severe headaches, among other side effects. In the second box, provide the structure of monosodium glutamate, the sodium salt of the singly deprotonated form of glutamic acid.

(iii) In the third box, provide the major form of glutamate, as it would exist at a pH of 7 (in your liver cells).

(i) assign pK_a values



glutamic acid

(ii) monosodium glutamate

(iii) glutamic acid at pH 7

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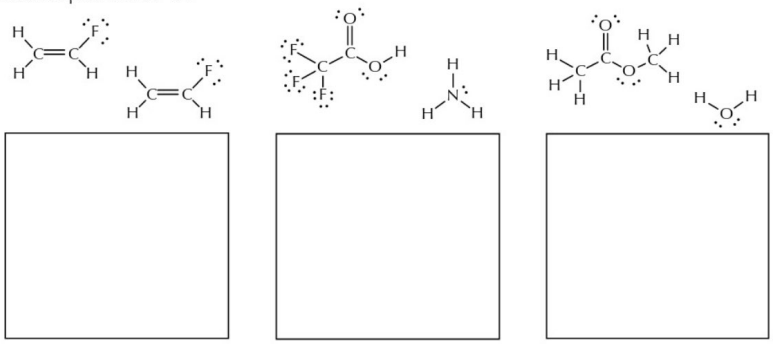
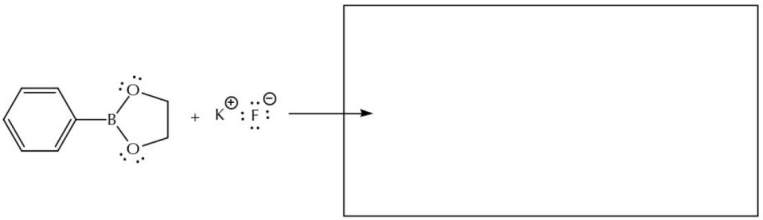
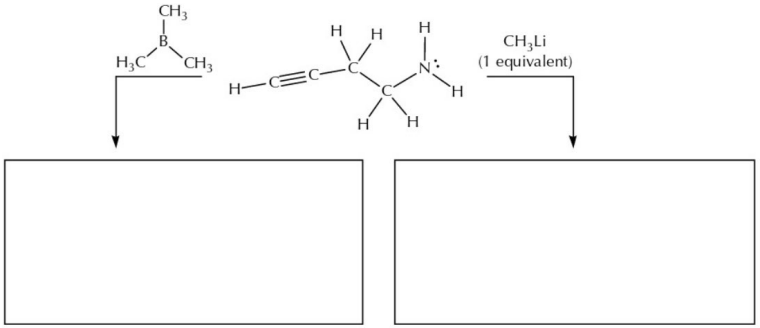
3.43 For each the following pairs of molecules, either (a) a hydrogen bond is expected to form between them, (b) a proton transfer reaction is expected to happen between them, or (c) neither of these is expected. Predict which of these outcomes is predicted for each of the pairs. For an expected hydrogen bond, redraw the compounds in the space and show the hydrogen bond as a dashed line. For a proton transfer reaction, show the curved arrow mechanism on the compounds and then draw the products in the space. If neither of these outcomes is expected, mark the space with an "X".



3.44 Predict the structure of the product in the following chemical reaction (make sure the equation is balanced).



3.45 Predict all of the products for each of the following reactions. Be sure to balance the equations.



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The Chemical Laboratory at the University of Michigan.

Chemical History at the University of Michigan

Built in 1856, this was the first chemical laboratory at a state university: Its one-story structure contained three rooms and was equipped with 26 laboratory tables. The construction cost was about six thousand dollars, including the building and its equipment. Chemistry teaching had begun at U-M in 1844, but with no laboratory component.

The first teaching laboratory for chemistry in the U.S. was built at Yale University in the 1940s, and both that one and the one at U-M were modelled on Justus von Liebig's laboratory in Giessen, Germany. The U-M building served medical students and the chemistry faculty as both laboratory and classroom. The building was situated in roughly the southeast corner of the grassy area of the current campus Diag.

Multiple additions were made to the building throughout the late 1800s, including a three-story wing in 1890. Chemistry and Pharmacy moved to their new building in 1908 (the 1908 building still stands at the western side of the interconnected set of three structures that house the departments of chemistry and biophysics today). After the 1908 move, the 1856 building, and all its additions, was occupied by the department of economics until 1981, when the entire complex was destroyed in an arson fire on Christmas Eve.

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CHAPTERS 1–3

Exam Questions

The first midterm examination in the first-term organic chemistry course at the University of Michigan typically has five pages of questions that integrate the topics from Chapters 1–3.

The following pages of "Exam Questions" (EQ 01.01 – EQ 01.30) were used in examinations between 1998–2018.

The 5-page examinations are laid out for a 60-minute time period, and students have 90 minutes to take the tests.

Any set of five pages from this group of 30 questions might be used to create a practice exam.

Select any five of these pages and time yourself for 90 minutes, without accessing any resources, to self-test your mastery of the main topics from Chapters 1–3.

Chapter 1

- Principles of organic reactions
  - Balanced equations
  - Predictable and regular bonding in organic main group elements
  - Reactions tend to be subtle and not dramatic reorganization of just a few bonds
- Molecular formulas, line abbreviation drawings & units of unsaturation, structural isomers
- Reactivity of open shell atoms
- Curved arrow notation

Chapter 2

- Delocalization in organic molecular structures
  - Identifying localized and delocalizable electrons
  - Drawing and evaluating resonance contributors
- Bonding and molecular geometry
  - VSEPR
  - Hybridization
  - Creating 3D orbital drawings
- Structure and properties
  - Bond lengths
  - Bond and molecular dipoles
  - Hydrogen bonding

Chapter 3

- Lewis acid-base definitions and reactions
- Bronsted acid-base definitions and reactions
  - Evaluating the position of an acid-base equilibrium using principles
  - Quantitative pK_a scale, and structural trends that explain acid-base strength
  - Using the pK_a scale to predict and evaluate reactions
  - Relationship between pH and the composition in solution

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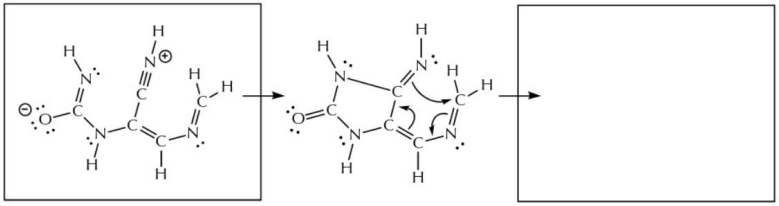
EQ 01.01

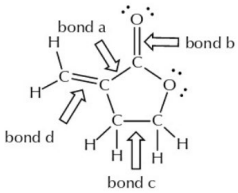
A. The curved arrow notation is a powerful tool because it communicates chemical information for experienced and inexperienced readers alike. For the following example (based on *J Org Chem*, **2001**, *66*, 8436):

(a) provide the curved arrows that lead to the structure drawn in the center

(b) provide the closed shell atom structure that follows from the curved arrows



B. α-Methylene-γ-butyrolactone is one of the compounds that gives the red American rose its distinctive odor. Rank the 4 bonds (a-d) in the anticipated order of bond length.



α-methylene-γ-butyrolactone

longest bond:

shortest bond:

C. This question is based on some unfamiliar chemistry. A bit of logic and the details provided in the description are necessary to be able to solve this. Chlorobenzene combines in a 1:2 ratio with lithium metal. The outcome is one equivalent of lithium chloride plus a new compound whose structure can be deduced from the information provided here. In particular, the new compound that forms undergoes a Brønsted acid-base reaction with water to give benzene plus lithium hydroxide. What is the structure of the compound that satisifies all of these criteria?

chlorobenzene

plus $Li^{\oplus}\ :\ddot{Cl}:^{\ominus}$

benzene

plus $Li^{\oplus}\ :\ddot{O}-H$

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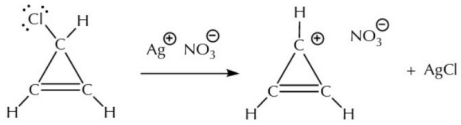
EQ 01.02

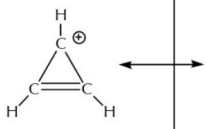
When 3-chlorocyclopropene (compound A) reacts with silver nitrate ($AgNO_3$), an ionic compound with an open shell carbon cation (known as a carbocation) is formed. One of the resonance contributors of cyclopropenium nitrate, compound B, labelled B-1, is shown below.



compound A

resonance contributor B-1 for compound B

(a) The actual molecular structure of the carbocation (B) is best described by three resonance contributors. Draw the other two resonance contributors.



contributor B-1

contributor B-2

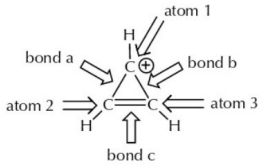
contributor B-3

(b) The significance of B-1 is [greater than / the same as / less than] that of B-2 in describing the actual structure of B.

(c) The significance of B-1 is [greater than / the same as / less than] that of B-3 in describing the actual structure of B.

(d) The significance of B-2 is [greater than / the same as / less than] that of B-3 in describing the actual structure of B.

Labels for bonds and atoms in B. Contributor B-1



(i) Using lines, dashes and wedges for sigma bonds and the direction of nonbonding electron pairs, p orbitals for lone p orbitals and overlapped p orbitals for pi bonds, draw a three dimensional orbital picture for resonance contributor B-1.

What are expected hybridizations for:

(e) atom 1 (f) atom 2 (g) atom 3

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EQ 01.03

The ionic substance sodium borohydride $NaBH_4$ (which is the sodium cation plus the borohydride, $BH_4^{\ominus}$ anion) is a commonly used chemical reagent in organic chemistry. It can be prepared by taking the ionic substance sodium hydride (NaH) and combining it with borane (BH_3).

(a) Draw the ionic compound, sodium hydride (NaH). Include any nonbonding electrons and formal changes, as necessary.

(b) What is the anticipated hybridization for the boron atom in borane (BH_3)?

(c) Draw a representation for the three-dimensional structure for BH_3 according to the hybridization model for bonding. Show any nonbonding electrons and formal charges; use lines, dashes, and wedges for sigma bonds, and p orbitals for any isolated p orbitals or pi bonds.

(d) Using Lewis structures, provide the complete, curved arrow mechanism for the reaction between sodium hydride (ionic NaH) and borane (BH_3) to produce sodium borohydride (ionic $NaBH_4$).

redraw NaH and BH_3, plus the curved arrow mechanism	provide the structure for $NaBH_4$

(e) What is the anticipated hybridization for the anion in the ionic compound, $NaBH_4$?

(f) Draw a representation for the three-dimensional structure of the anion in $NaBH_4$ according to the hybridization model for bonding. Show any nonbonding electrons and formal charges; use lines, dashes, and wedges for sigma bonds, and p orbitals for any isolated p orbitals or pi bonds.

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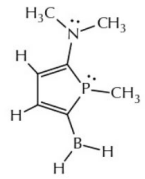
EQ 01.04

A. In an article that reported on the "Structure-Property Relationship in Phosphole Monomers" (*J Org Chem*, **2000**, *65*, 2631), chemists were interested in the contribution of various resonance forms to the actual structure of compound C, below, among others.

(a) Draw the other two significant resonance forms for this compound (all atoms closed shell, with formal charges -1, 0, +1).

resonance contributors for compound C



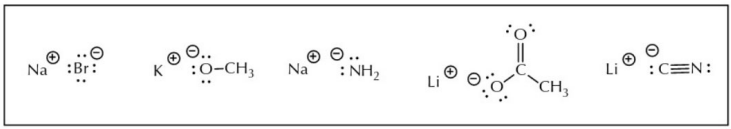
resonance contributor C1 | resonance contributor C2 | resonance contributor C3

(b)

Which of these three resonance forms contributes least to the actual structure?	Provide a brief explanation of your choice.
C1 C2 C3	

B. Including any formal charges, using lines, dashes, and wedges to represent sigma bonds and the directionality of nonbonding electrons, and using overlapping p orbitals for pi bonds, draw a representation for the three-dimensional orbital structure of carbon monoxide (CO; all closed shell atoms).

C. (a) Using a 1:1 molar ratio, which one of the following bases could be used to completely deprotonate butanol ($CH_3CH_2CH_2CH_2OH$), $K_{EQ} > 10^3$?



(b) Using Lewis structures, show the balanced chemical equation between butanol and the base that you selected in part (a). Include the curved arrow mechanism in your equation.

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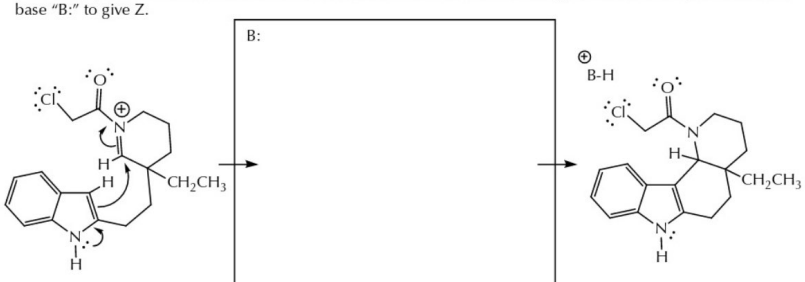
EQ 01.05

A. Complete the following step, which was reported for the synthesis of Aspidospermine (a biologically interesting compound; *J Org Chem*, **2000**, *65*, 2642). In the space, place the single structure Y implied by the mechanistic arrows associated with structure X (Y has all closed shell atoms). By examining the structure of the ultimate product Z, you should also be able to draw the mechanistic arrows needed to go from structure Y, with Bronsted base "B:" to give Z.



structure X | structure Y | structure Z

B. The amino acid called tyrosine is shown (below) in the form that would be expected at a pH < 1 (i.e., the fully protonated form). Titration of tyrosine with base reveals three acidic protons with pK_a values of 2.20, 9.11, and 10.07.

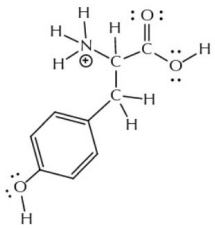
(a) Circle the proton that would be removed first when tyrosine is titrated with base.

(b) Which pK_a value corresponds to the first proton that is removed with bases?

circle one:	2.20	9.11	10.07

(c) Draw the structure of the major form of tyrosine that would exist at a high pH (>11), after all three of the most acidic protons have been removed by base. Indicate nonbonding electrons and formal charges, as needed.

tyrosine at pH < 1



Circle the proton that would be removed first when histidine is titrated with base.

tyrosine at pH > 11

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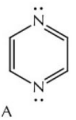
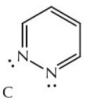
EQ 01.06

Rank each of the following sets of molecules according to the criteria indicated.

(a)


A

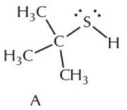
B

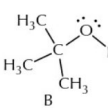

C

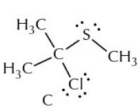
dipole moment

□ highest > □ > □ lowest

(b)


A


B


C

strongest hydrogen bond acceptor

□ > □ > □

(c)

$C_3H_7NO_3$ A

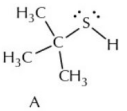
$C_6H_9BrO_2$ B

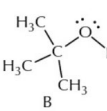
C_3H_2OS C

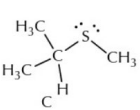
units of unsaturation

□ highest > □ > □ lowest

(d)


A

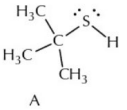

B

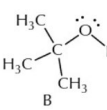

C

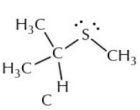
with respect to the lowest pK_a in each of the 3 molecules

□ highest value > □ > □ lowest value

(e)


A

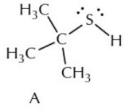

B

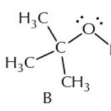

C

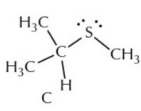
strongest hydrogen bond donor

□ highest > □ > □ lowest

(f)


A

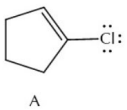

B

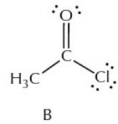

C

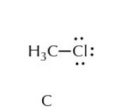
anticipated water solubility

□ highest > □ > □ lowest

(g)


A


B


C

C-Cl bond polarity

□ highest > □ > □ lowest

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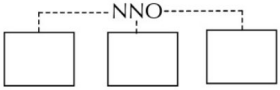
EQ 01.07

Nitrous oxide (N_2O) is a strong greenhouse gas that also has a significant impact on the chemistry of the troposphere and stratosphere. It has 200–300 times more warming potential than carbon dioxide (*J Org Chem*, **2001**, *66*, 6096).

(a) Given the NNO connectivity of nitrous oxide, draw the set of two resonance contributors that define its structure. These should be Lewis structural representations with all closed-shell atoms and formal atomic charges of -1, 0, and +1; nonbonding electrons should be included.

(b) In the space above, circle the resonance contributor that is predicted to be the major resonance contributor to the actual structure of N_2O and write "major" beneath it. Describe briefly the reason for your selection.

(c) Remembering that these multiple resonance forms imply a single molecular structure. What are the hybridizations you would predict for the three atoms in N_2O?



(d) Provide a three-dimensional orbital drawing for the two resonance forms that you drew as the contributors to the structure in part (a).

Represent sigma bonds and the directionality of localized nonbonding electron pairs with lines, dashes, and wedges, and use p orbitals to represent pi bonds (show overlap) or electron pairs that are delocalized.

major contributor

minor contributor

(e) What is the overall, anticipated observable molecular geometry for N_2O?

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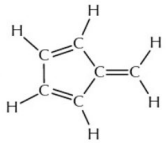
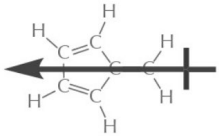
EQ 01.08

A. Although the following Lewis structure is the only resonance form for compound R that has all of its atoms with closed shell electron configurations, important physical and chemical properties for this molecule are explained by resonance forms that include an open shell atom. For example, the measured dipole moment for compound R is surprisingly large. A representation for the direction of the molecular dipole moment, which lies along the symmetrical molecular axis, is also shown below.

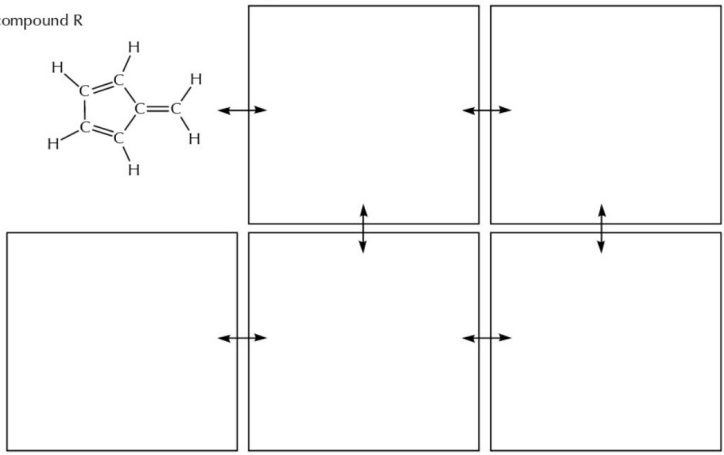
compound R



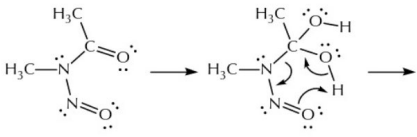


Draw the complete set of 5 resonance forms for compound R (in addition to the one shown here) that are consistent with the unusually high molecular dipole moment and its direction.

compound R



B. *N*-Nitrosamines and *N*-nitrosamides have been studied extensively because they are suspected as cancer causing agents (*J Org Chem*, **2001** *66*, 5790). One of the pathways by which N-nitrosamide (compound S) becomes chemically active is shown below. Show the structures of the products implied by the curved arrow mechanism starting from compound T.



compound S compound T

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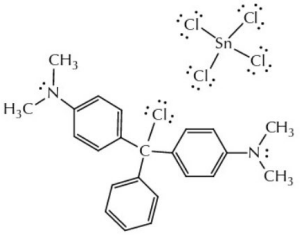
EQ 01.09

A. The year 2001 was the 100th anniversary of the discovery of carbocations. The cationic dye, malachite green, is one of the earliest organic dye materials (*J Org Chem*, **2001**, *66*, 5943). Provide the curved arrow machanism as well as the structure of the complex formed when tin tetrachloride ($SnCl_4$) is combined with compound D. Like certain other metal atoms, the tin atom in tin tetrachloride behaves as an open shell (Lewis acidic) atom towards Lewis bases. Follow the reaction outcome, as drawn, and complete the question as directed in the spaces.

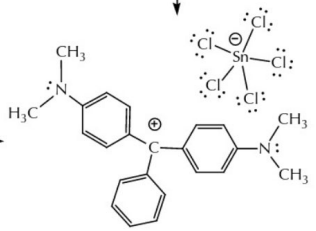
provide the curved arrow mechanism:



compound D

provide the structure of the complex formed between $SnCl_4$ and compound D as well as the curved arrow mechanism required to give malachite green (see below):

provide one of the two most significant resonance contributors to the malachite green structure:



malachite green

B. In the structure of solid water (ice), each water molecule is surrounded by four others. Using lines, dashes, and wedges to represent sigma bonds and the directionality of nonbonding electrons, draw a three-dimensional picture for a water molecule. Now surround your first water molecule with four other water molecules, and represent the strong intermolecular interaction that is expected between each of these water molecules and your original with a single dashed line (||||||||) between the atoms that are most closely associated. The four additional water molecules do not need to be shown as three-dimensional drawings.

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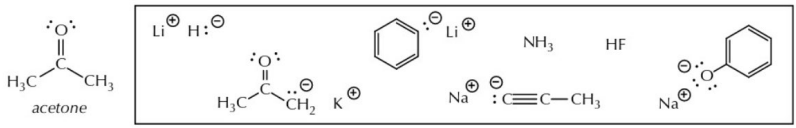
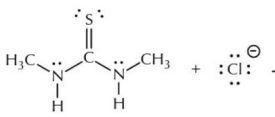
EQ 01.10

A. Acetone has an observed pK_a of 19. Which of the following could be used as a base to deprotonate acetone with a $K_{EQ} > 10^3$? Circle all that apply.



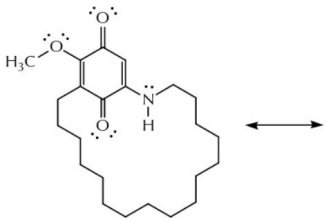
B. Reactions that produce chloride ion as a product can be shifted to the right (Le Châtelier's Principle) by adding thiourea DM (*J Am Chem Soc*, **2014**, *136*, 12872) to the reaction mixture. It is proposed that each thiourea DM forms two strong hydrogen bonds with a single chloride ion. Using dashed lines (||||||||||) to represent the interaction between the donor/acceptor sites, draw a picture of the two anticipated interactions between a thiourea DM molecule and a chloride ion. As always, be sure to include formal charges and nonbonding electrons.



thiourea DM

C. Geldanamycin is a potential anticancer agent that interferes with cell proliferation. An extremely simplified version of geldanamycin (compound GS) was observed to supress the peroxidation of lipids and maintain cell viability. There are a number of other resonance contributors for compound GS, although the one shown below is the most significant contributor.

Draw the structure of the next most significant resonance contributor to the structure of compound GS. Include all nonbonding electrons and formal charges, as needed, in your drawing (*ACS Med Chem Lett*, **2013**, *4*, 953).



compound GS

this is the most significant resonance contributor to the structure of compound GS

Note: there are 16 "CH_2" groups in that large ring of atoms; be sure you draw/count them carefully!

provide the next most significant resonance contributor to the structure of compound GS

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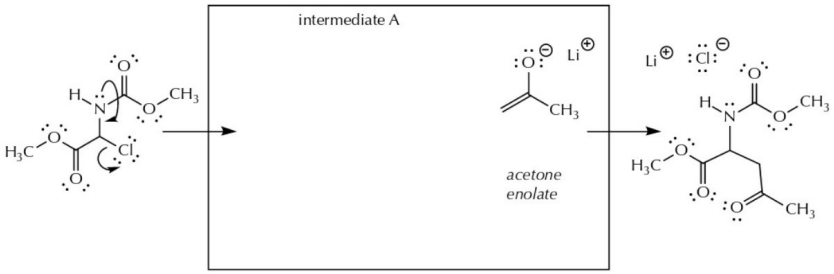
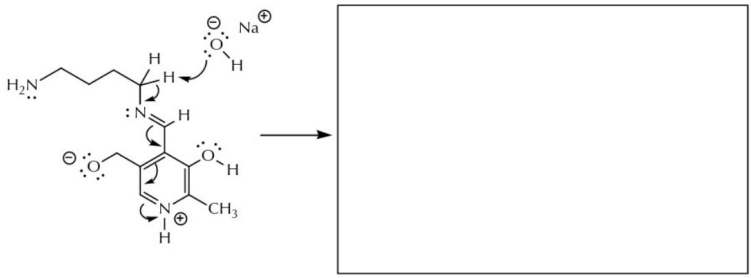
EQ 01.11

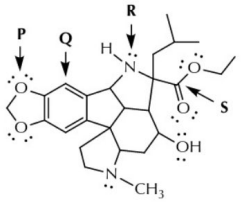
A. In 1912, Carl Mannich, a Professor of Pharmaceutical Chemistry at the University of Göttingen, published a paper on a reaction that would come to bear his name: The Mannich Reaction (*Archiv der Pharmazie*, **1912**, *250*, 647). In the following problem, (a) provide the structure of the intermediate (A) that results from the curved arrows shown. Then, (b) using your intermediate, provide the arrows that are needed when intermediate A reacts with acetone enolate to give the observed products.



B. The biological preparation of nicotine, in some plants, uses a Mannich reaction as one of the key steps. Early in the preparation of nicotine, the following reaction is observed. Provide the structures that result from the curved arrow mechanism. Include all necessary nonbonding electrons and formal charges. Provide the balanced equation.



C. The Mannich reaction has a long history of use in the synthesis of complex molecules found in nature, commonly referred to as natural products. The synthesis of gracilamine (structure shown below) employed a Mannich reaction in its synthesis (*Angew Chem Int Ed*, **2014**, *53*, 9539). For the four designated atoms in gracilamine (atoms **P** through **S**), provide the hybridization, electronic geometry, and observable geometry. Gracilamine is isolated from plants in the *Amaryllidaceae* family, found on certain mountains in Turkey.



gracilamine

	hybridization	electronic geometry	observed geometry ("n/a" if not observable)
P			
Q			
R			
S			

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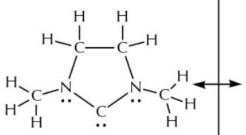
EQ 01.12

N-Heterocyclic carbenes (*Org Lett*, **2014**, *16*, 4742) are a unique and useful class of small, organic molecules. They contain a carbon atom that has both an open shell and a nonbonding electron pair (see resonance contributor A). One reason that these unusual molecules are stable is because the structure of the molecule is best described by two other resonance contributors, B and C, both of which have all atoms with closed-shell electron configurations.

(a) Provide drawings for the two resonance contributors, B and C, that satisfy the stated conditions. Be sure to show all nonbonding electron pairs and/or formal charges, as needed.



resonance contributor A | resonance contributor B | resonance contributor C

(b) Is resonance contributor A a more, less, or equally significant contributor to the structure compared with contributors B and C?

(c) Is resonance contributor B a more, less, or equally significant contributor to the structure compared with contributor C?

(d) The conjugate acid for this N-heterocyclic carbene has a pK_a value of about 18, so the protonation reaction with HCl is quite favorable. Considering the information you learn about its structure thanks to its resonance contributors, draw the structure of the conjugate acid for this N-heterocyclic carbene. The product of the balanced equation of the reaction with HCl should be shown, and the structure should have all closed shell atoms. Include nonbonding electrons and formal charges, as needed.

(e) Provide a 3D orbital drawing for resonance contributor A.

(i) use lines, dashes, and wedges for sigma bonds and the directionality of localized nonbonding electrons, and p orbitals for pi bonds (indicate the overlap) and delocalizable nonbonding electrons for all of the atoms

(ii) be sure to account for the expected hybridizations

(iii) although you have a number of choices, you should make the drawing where all of the carbon and nitrogen atoms are in the plane of the page

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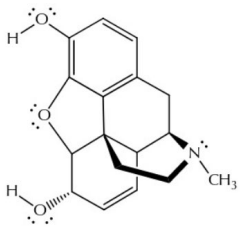
EQ 01.13

A. Opiods are an example of narcotics, drugs that induce "sleep" or "numbing" effects. The term derives from opiates, referring specifically to drugs derived from the opium poppy, including morphine, codeine, and thebaine. The use of these substances predates recorded history. The structure for morphine is shown here. Morphine has one best hydrogen bond donor site and one best hydrogen bond acceptor site. Add two molecules of water to this drawing, and indicate these two most favorable interactions.



morphine

B. Although the reaction between diisopropyl amine (pK_a 35) and sodium hydride (NaH) gives a conjugate acid whose pK_a is nearly identical to that of the diisopropyl amine, the reaction can be confidently predicted to go to completion (all the way to the right) as shown below. Briefly explain this observation.

$$[(CH_3)_2CH]_2NH + NaH \longrightarrow [(CH_3)_2CH]_2NNa + HH$$

C. There are a number of $C_4H_6Cl_2$ structural isomers containing a carbon-carbon double bond as the unit of unsaturation. What is the Lewis structure for one of the double-bond containing $C_4H_6Cl_2$ isomers with no anticipated dipole moment? Note: As with all considerations of dipole moment, you need to take the molecular geometry into account.

D. Draw the Lewis structure for a C_4O_4 isomer with the following properties:

(a) all closed shell atoms
(b) all atoms uncharged
(c) no molecular dipole moment
(d) decomposes readily to give 4 CO molecules

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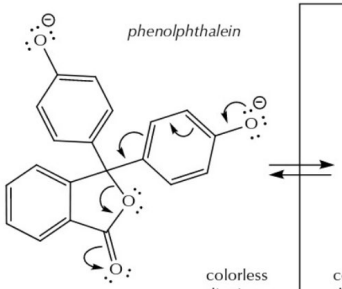
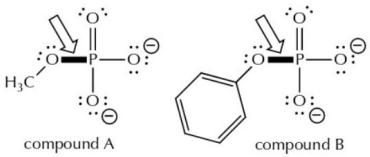
EQ 01.14

A. Phenolphthalein is a sensitive pH indicator with the formula $C_{20}H_{14}O_4$. Often used in titrations, it turns from colorless in acidic solutions to pink in basic solutions, the color change occurring between pH 8 and pH 10. If the concentration of indicator is particularly strong, it can appear purple. The color is due to the following structural equilibrium on the dianion that forms under basic conditions (*J Org Chem*, **2005**, *70*, 4609). Draw the structure of the colored dianion based on the following mechanism.



B. The effect of delocalization on structure and reactivity is still an area of active study. In 2005, a report on the following pair of moleules (plus others) was published (*J Org Chem*, **2005**, *70*, 4805). The authors predicted that the bond indicated by an arrow would be longer in compound B than it would be in compound A. Explain why this is a reasonable prediction, and provide a key resonance form that supports the argument.

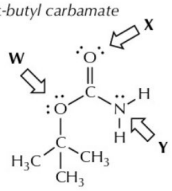


a key resonance contributor

brief explanation

C. Carbamates are functional groups that have many applications in the preparation of peptides, proteins, and other important natural products. They are also found in agrochemicals such a pesticides. The structure of *tert*-butyl carbamate is shown. Based on this and its other significant resonance forms containing all closed shell atoms, answer the following about the three labeled atoms (**W**, **X**, and **Y**) of *tert*-butyl carbamate.

tert-butyl carbamate



	VSEPR (electronic) geometry	observable geometry (or "none")	hybridization
W			
X			
Y			

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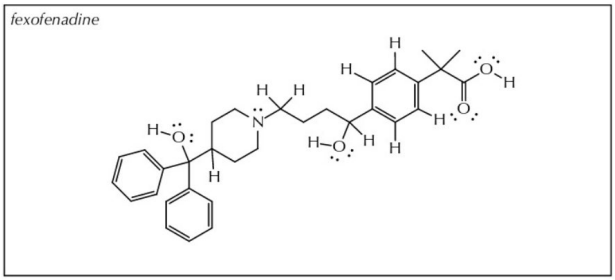
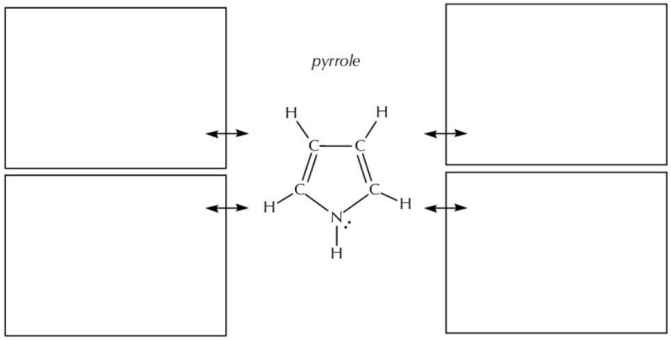
EQ 01.15

A. Fexofenadine is a nonsedating allergy medicine sold under the trade name "Allegra."
(a) Draw an arrow pointing to the most Brønsted basic atom in this molecule.
(b) Draw a square around the most Brønsted acidic proton in this molecule.
(c) Circle the shortest bond (i.e., both atoms plus the bond) in this molecule.

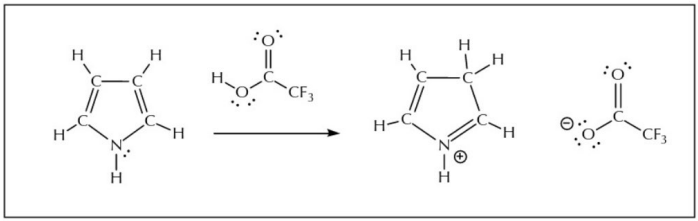


B. Pyrroles are components of larger aromatic rings, including the porphyrins of heme, in hemoglobin, the chlorins and bacteriochlorins of chlorophyll, and the corrin ring of vitamin B_{12}.

(a) Draw the four other resonance structures for pyrrole that have all closed shell atoms and formal charges of -1, 0, or +1.



(b) When trifluoroacetic acid is mixed with pyrrole, the following product is observed. Provide the curved arrow mechanism that accounts for this reaction.



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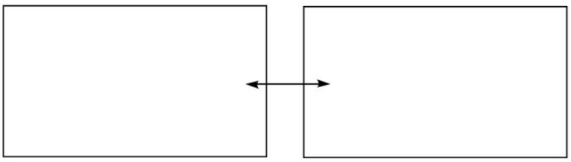
EQ 01.16

Ozone (O_3) is formed in the upper atmopshere, resulting from the absorption of ultraviolet light from the sun by molecular oxygen. Its name is derived from a Greek word meaning "to smell," because of a characteristic odor in the air following lightning strikes. The gas was isolated and characterized in the early to mid-1800s.

(a) The connectivity of ozone is OOO. Its dipole moment (0.53 Debye) is consistent with a bent molecule. Ozone has all closed shell atoms and its structure can be represented by two equally significant resonance contributors. Draw them.



(b) What are the hybridizations of the oxygen atoms in ozone? Place the labels near the atoms in both of your resonance contributors.

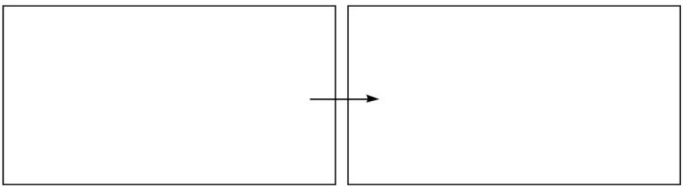
(c) Provide the 3D orbital drawings for the ozone resonance contributor in the left-hand space. Use lines, dashes, and wedges for the localized electron structure, including sigma bonds and the direction of nonbonding electron pairs. Use p orbitals for pi bonds (overlapped) as well as for delocalizable electron pairs.

(d) Based on its molecular formula, a possible structure for ozone might be a three-membered ring of oxygen atoms. (i) What experimental evidence is inconsistent with this structure? (ii) Is this structure also a resonance contributor (why or why not)? (iii) Starting from the hypothetical three-membered ring structure, provide the curved arrow mechanism that converts it to one of the two resonance contributors in part (a).

(i)

(ii)

(iii)



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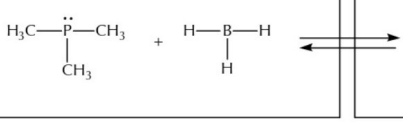
EQ 01.17

A. (a) Predict the product of the following reaction. Provide the curved arrow notation for the mechanism.



(b) Using lines, dashes, and wedges for sigma bonds, as well as for indicating the directionality of non-bonding electron pairs, and using overlapped p orbitals for pi bonds as well as filled or empty lone p orbitals as necessary, provide a 3D orbital drawing for BH_3.

(c) If trimethylamine [$(CH_3)_3N$:] was used in place of trimethylphosphine [$(CH_3)_3P$:] in the chemical reaction in part (a), and presuming the concentrations and other reaction conditions are kept the same, do you predict that the equilibrium constant for the reaction with trimethylamine will be a larger, smaller, or the same value as the one with trimethylphosphine? Briefly explain your answer.

The K_{EQ} for the reaction with [$(CH_3)_3N$:] is greater than less than that same as the K_{EQ} for the reaction with [$(CH_3)_3P$:].	explain:

B. When formaldehyde ($H_2C{=}O$) and ammonia (NH_3) are combined, a new compound (compound A: $C_3H_9N_3$) forms, along with some water. The balanced equation is shown here:

$$3\ H_2C{=}O + 3\ NH_3 \longrightarrow \underset{\text{compound A}}{C_3H_9N_3} + 3\ H_2O$$

Compound A, when treated with a special form of nitric acid, gives RDX (Royal Demolition eXplosive, which is 150 times more potent than TNT, the principal explosive in dynamite). The successful synthesis of RDX was worked out at the University of Michigan in the 1940s, by Professor Werner Bachmann, as a part of the WWII defense effort.

What is the structure of compound A?

Here are some facts about compound A

(1) its molecular formula is $C_3H_9N_3$

(2) its molecular dipole moment equals zero

(3) it is soluble in water

(4) it has a pK_a about the same as ammonia

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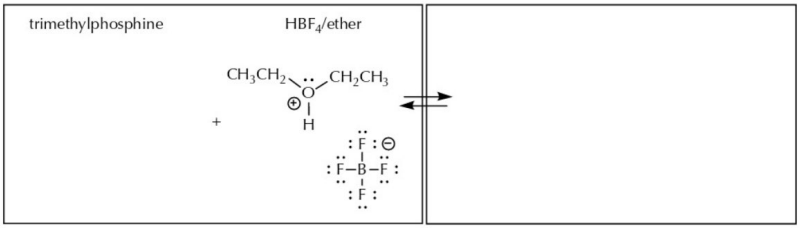
EQ 01.18

Trimethylphosphine [$(CH_3)_3P$] is an extremely air sensitive liquid; in fact, it will combust spontaneously when it is exposed to oxygen in the air. However, when trimethylphosphine reacts with a solution of tetrafluoroboric acid (HBF_4) in ether ($CH_3CH_2OCH_2CH_3$), the trimethylphosphine is converted into an air-stable, easily handled solid. The HBF_4/ether combination is itself a solution of an ionic compound resulting from an acid-base reaction.

(a) Draw the complete Lewis structure for trimethylphosphine.
(b) Predict the product of the reaction between trimethylphosphine and HBF_4/ether.
(c) Provide the curved arrow mechanism for the reaction between trimethylphosphine and HBF_4/ether.



(d) Although trimethylamine [$(CH_3)_3N$] is in the same chemical family as trimethylphosphine, its reactivity is significantly different. Its reaction with oxygen, for example, does not give spontaneous combustion. It does react slowly with oxygen, however, to give trimethylamine oxide [$(CH_3)_3NO$]. Draw the complete Lewis structure for trimethylamine oxide.

(e) The reaction product between trimethylphosphine and oxygen is trimethylphosphine oxide [$(CH_3)_3PO$]. There are two resonance forms used to represent the structure of $(CH_3)_3PO$ because phosphorus can have an expanded shell electronic structure. What are these two resonance contributors?

(f) Trimethylamine oxide, which you drew in part (d), cannot be represented by a comparable pair of resonance forms, but rather by only one structure (hopefully the one you have drawn correctly in part (d)). State briefly why there is not a second resonance structure for trimethylamine oxide.

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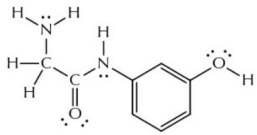
EQ 01.19

A. Some organic molecules dissolve in water because they undergo an actual chemical reaction that first turns them into ions, much the same way ionic solids dissolve by separating into discrete ions. One such organic molecule is called *tert*-butyl bromide. Given the information below, (a) provide the curved arrow notation for the mechanism of the first step. (b) Show the pair of ions that forms when *tert*-butyl bromide dissolves into water. (c) The subsequent outcome, which involves the combination of one of the ions with a water molecule, is shown on the right; provide the curved arrow notation for its formation.

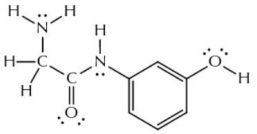
tert-*butyl bromide*

B. Follow the direction in each of the answer spaces concerning the chemistry of this molecule.

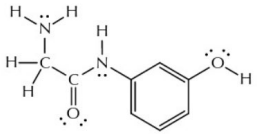
Put a circle around the hydrogen atom with the lowest pK_a value.



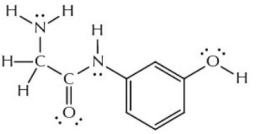
Draw a water molecule that is hydrogen bonded to the best anticipated hydrogen bond acceptor.



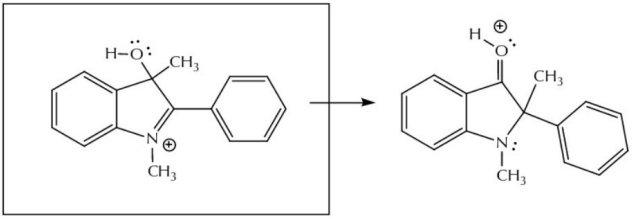
Draw a water molecule that is hydrogen bonded to the best anticipated hydrogen bond donor.



Put a circle around the pair of atoms with the shortest bond length.



C. Provide the curved arrows that account for the one-step mechanism of the following isomerization reaction.



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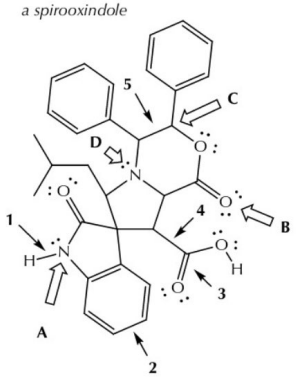
EQ 01.20

A. Spirooxindoles are key intermediates used in the synthesis of several therapeutic agents.

a spirooxindole



(a) Assign the best hybridizations, electronic (VSEPR) and observable geometries for the atoms listed below. If a geometry or hybridization cannot be assigned, write "N/A".

	hybridization	VSEPR (electronic) geometry	observable geometry
A			
B			
C			
D			

(b) Bonds **1**-**5** are different lengths. Rank them in order of longest to shortest.

longest > > > > shortest

(c) How many units of unsaturation does the above spirooxindole have?

B. There are several structures that can be drawn with the molecular formula C_3H_5NO. Using complete Lewis structures with all closed shell and uncharged atoms, draw one isomer that fits each of the following criteria (there may be more than one correct isomer for each description).

Contains a four membered ring. The oxygen and the nitrogen atoms both include hydrogen bond donors and hydrogen bond acceptors.

Contains a five membered ring. No hydrogen bond donors. The oxygen is sp^2 hybridized.

Does not contain a ring. The nitrogen atom includes a hydrogen bond donor, but oxygen does not. The nitrogen is sp^3 hybridized. One carbon is sp hybridized.

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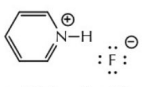
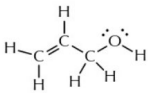
EQ 01.21

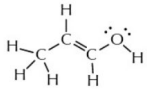
A. Pyridinium fluoride (shown below) is a Brønsted acid. Which of the three C_3H_6O isomers is most likely to be protonated at its oxygen atom by pyridinium fluoride? Briefly state why.



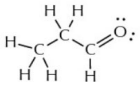
pyridinium fluoride



isomer X



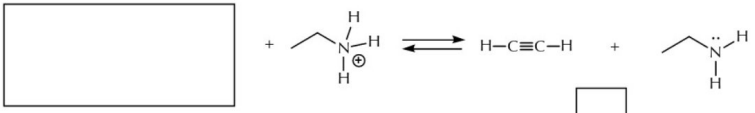
isomer Y



isomer Z

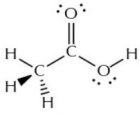
Which isomer is most likely to be protonated? *isomer* X Y Z	Explain:

B. Fill in the missing information from the following reaction scheme.

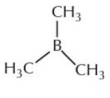


Estimate the value of the K_{EQ} for the reaction, as shown. $K_{EQ} = 10$ ☐

C. When one molecule of trimethylborane $[B(CH_3)_3]$ reacts with one molecule of acetic acid, the borane will preferentially undergo a complexation reaction with only one of the oxygen atoms in acetic acid. Draw the two possible complexation products in their appropriate spaces ("favored" and "unfavored"), and provide an explanation for the choice.



acetic acid



trimethylborane

favored	unfavored

explanation (use words and pictures)

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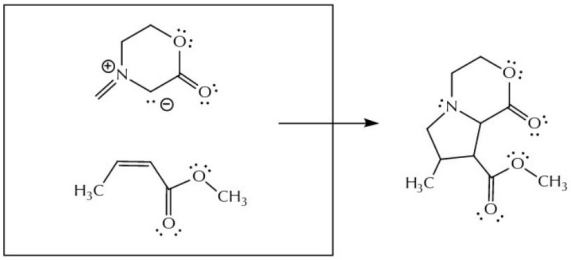
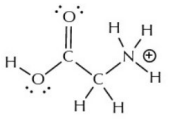
EQ 01.22

A. Complex molecules can be prepared through what are called cycloaddition reactions, in which two halves of a desired structure combine to give new rings. Provide the curved arrow mechanism for this one-step cycloaddition reaction.



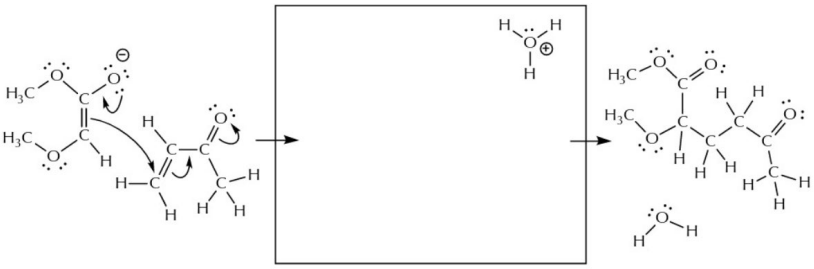
B. The structure of glycine, one of the 20 naturally occuring amino acids, is shown below as it appears when in a solution of pH = 0.

Assuming the hybridization model for all atoms and considering all resonance contributors, provide an accurate and complete 3D orbital picture for glycine. Use lines, dashes, and wedges for sigma bonds and the directionality of localized electron pairs, p orbitals (lone or overlapping) for pi bonds and delocalizable electron pairs. All bond angles should reflect appropriate geometry and hybridization chosen for your drawing.



glycine, at pH = 0

C. When chemists discover a reaction that is particularly unique or useful, they will often have the reaction named after them. One such "name reaction" is the Michael reaction, which was first reported by Arthur Michael in about 1880. The following Michael reaction, which is used in the synthesis of a therapeutic medicine, is a two-step reaction featuring a formation of a carbon-carbon bond followed by an acid-base reaction. In the space provided, draw the intermediate resulting from the first step of the reaction, as well as the curved arrow mechanism for the acid-base reaction between the intermediate and hydronium ion to give the observed product.



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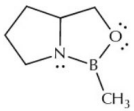
EQ 01.23

Organoboranes, such as the one shown below, are useful in carrying out organic syntheses (*J Am Chem Soc*, **2002**, *124*, 3808).

(a) Provide the two other resonance contributors for this compound (all atoms must be closed shell, formal charges between -1 and +1).

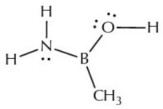


contributor R1 | contributor R2 | contributor R3

(b) Which of the three contributors would you predict to be most significant (circle more than one if they are equal contributors):

R1 R2 R3

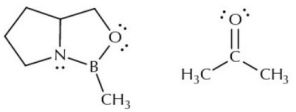
(c) Draw a 3D orbital picture for this simplified fragment of R1. Use lines, dashes, and wedges for sigma bonds and the direction of localized electron pairs, and p orbitals for pi bonds (overlapped), empty p orbitals, and/or delocalizable electron pairs. All bond angles should reflect the appropriate geometry and hybridization chosen for your drawing.



fragment of R1

(d) Organoboranes such as this react quickly in Lewis acid-base reactions. Provide the complete curved arrow mechanism and draw complete Lewis structures for the product(s) you would expect in this reaction.

curved arrow mechanism for Lewis acid-base reaction



product(s) predicted to form in this reaction

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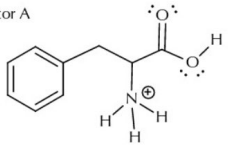
EQ 01.24

Phenylalanine is a naturally occurring amino acid. Its structure at pH = 0 is drawn below.

(a) Draw three other all closed shell atom resonance contributors, atoms with formal charges of -1, 0, or +1.

contributor A



phenylalanine (pH = 0)

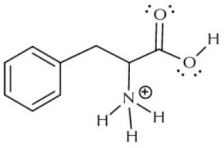
contributor B

contributor C

contributor D

(b) Rank the four resonance contributors in order of significance. Explain your reasoning.

(c) Based on the principle that the strongest hydrogen bond occurs between a hydrogen bond donor and an acceptor whose conjugate acid is closest in pK_a to the donor, show the strongest hydrogen bond expected between this form of phenylalanine and a water molecule.



(d) Draw the major form of phenylalanine as it would appear in solution at pH = 11.

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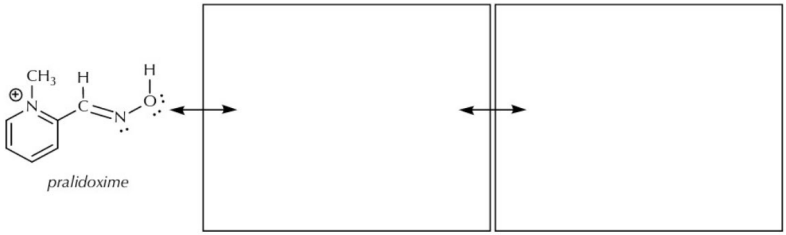
EQ 01.25

A. Pralidoxime is used with atropine as an antidote for nerve gas poisoning.

(a) Pralidoxime can be drawn with a set of three most signficant resonance contributors in which all atoms have closed shells and only one atom carries a positive formal charge. One is drawn for you; draw the others.



pralidoxime

(b) What is the expected observed geometry for the N atom outside of the ring?

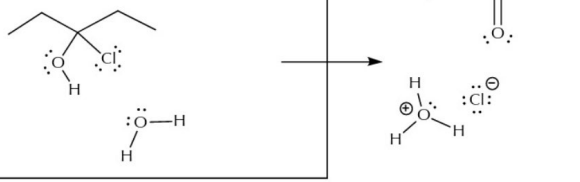
(c) What is the expected electronic geometry for the O atom?

(d) What is the expected hybridization of the N atom inside the ring?

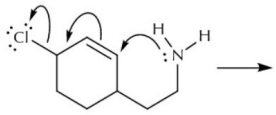
B. Provide the missing information for each of the following reactions, as directed.

(a)

Provide the curved arrow mechanism for the following one-step transformation.



(b)



Draw product(s) that result from the curved arrow mechanism.

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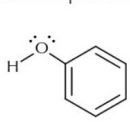
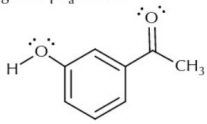
EQ 01.26

Estimating pK_a values from the pK_a table is always subject to variation when actual structures and/or actual experimental results are considered. The fundamental arguments used for analyzing organic structures should be used to explain any differences.

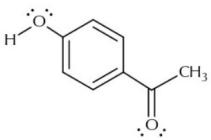
Both *meta*-hydroxyacetophenone and *para*-hydroxyacetophenone are observed to be more acidic than phenol, the closest model compound for estimating their pK_a values.



phenol
pK_a 10.0



meta-*hydroxyacetophenone*
pK_a 9.19

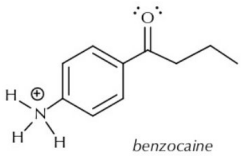


para-*hydroxyacetophenone*
pK_a 8.05

(a) In general terms, why do *meta*-hydroxyacetophenone and *para*-hydroxyacetophenone have lower pK_a values than phenol (use words and pictures)?

(b) Considering your explanation in part (a), why does *meta*-hydroxyacetophenone have a higher pK_a value than *para*-hydroxyacetophenone (use words and pictures)?

(c) Benzocaine, a common local anesthetic used in everything from cough drops to toothache remedies, either has a pK_a value of 2.5, 4.5, or 6.5. Using an appropriate model compound, and other knowledge gained in other parts of this question, deduce which pK_a is the actual one and explain why?



benzocaine

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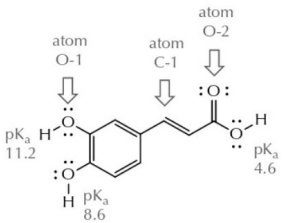
EQ 01.27

The following molecule (caffeic acid) is found in modest levels in apples, and somewhat higher levels in some herbs and spices (thyme, sage, spearmint, Ceylon cinnamon, and star anise). Plants use caffeic acid to make lignin, a complex polymer that is used to add rigidity to their cell walls.

Answer the following questions about caffeic acid.

caffeic acid



PLoS ONE 10(6):e0129963 (June 2015)

(a) How many delocalized electron pairs are in caffeic acid?

(b) Observable geometry at C-1?

(c) How many sp^3 hybridized atoms in caffeic acid?

(d) Electronic geometry at O-2?

(e) How many sp^2 hybridized atoms in caffeic acid?

(f) Observable geometry at O-1?

(g) What is the major form of caffeic acid expected to be present in a buffer solution of pH = 9?

Include nonbonding electron pairs and formal charges; counterions are not required.

(h) The two hydroxy (OH) groups on the benzene ring of caffeic acid (pK_a 8.6 and 11.2) differ in acid strength by almost a factor of 1000. In the presence of an added base, the proton with pK_a 4.6 is deprotonated first, then the one at pK_a 8.6. There is a single best resonance contributor for the resulting dianion that delocalizes the negative formal charge, resulting from deprotonation of the proton with $pK_a = 8.6$, onto another electronegative atom. Show that single resonance contributor.

(i) The pH of your body is about 7.4. What is the major form of caffeic acid expected to be present in a buffer solution of that pH value?

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EQ 01.28

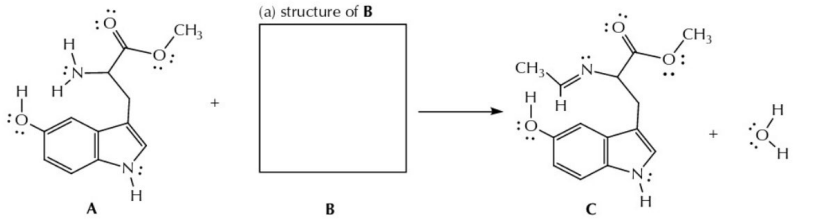
In 2012–13, a new class of biologically active compounds called hyrtioreticulins were isolated from marine sponges in Indonesia. The molecules can inhibit protein degradation, which can be potentially useful in medical treatments.

The following reactions were reported in a laboratory preparation of four different hyrtioreticulins (*J Nat Prod*, **2017**, *80*, 241).

(a) What is the structure of the missing reactant **B** (it has all closed shell atoms with no formal charges) that combines with **A** to give **C** plus one equivalent of water (this is a structural conclusion based on logic)?

(b) How many of the reagents listed can deprotonate ($K_{EQ} > 10^3$) **C** to give **D**?

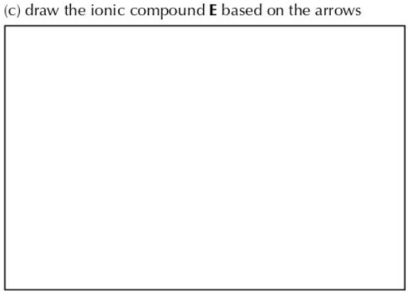
(c) Draw **E** based on the curved arrow mechanism shown with **D**. Compound **E** is an anionic compound whose atoms are all closed shell.



(b) mark with an "X" all that can deprotonate **C** ($K_{EQ} > 10^3$)

$NaNH_2$	$NaCCl_3$
NaCl	NaCN
NaOH	NaN_3

(c) draw the ionic compound **E** based on the arrows



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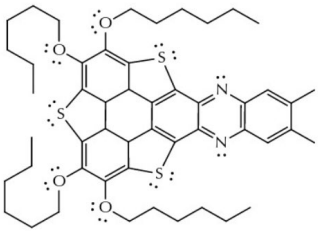
EQ 01.29

A. Trichalcogenasumanene ortho-quinones, such as compound A (shown below), are being investigated for their electronic properties, such as conductivity (*Angew Chem Int Ed*, **2017**, *56*, 1). Answer the following questions about the structure of compound A.



compound A

(a) How many delocalizable electron pairs?

(b) How many units of unsaturation? (hint: it's an even number)

(c) Hybridization for either of the nitrogen atoms?

For geometrical labels, write "N/A" if not observable.

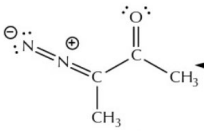
(d) Observable geometry for either of the nitrogen atoms?

(e) Electronic geometry for any of the sulfur atoms?

B. Diazo-carbonyl compounds, such as compound B (shown below) are being investigated for their ability to form carbon-carbon bonds in the production of new and interesting molecules (see, for example, iron carbenes reported in *J Am Chem Soc*, **2017**, *139*, 13624). Answer the following questions.

(a) Compound B has two other resonance contributors that have all closed shell atoms. Draw both of them, including all structural features such as nonbonding electrons and formal charges, as needed.

contributor B1 | contributor B2 | contributor B3



compound B

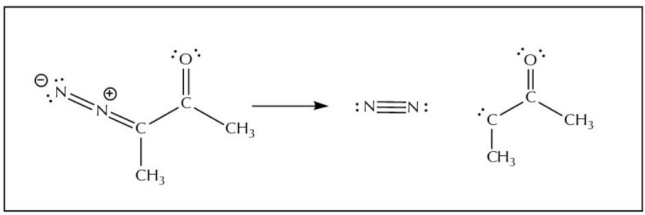
(b) Is contributor B2 more, less, or equivalent in significance to the structure of compound B than contributor B1?

circle one: more less equivalent

(c) Is contributor B3 more, less, or equivalent in significance to the structure of compound B than contributor B1?

circle one: more less equivalent

(d) Provide the curved arrows needed to account for the following observation:



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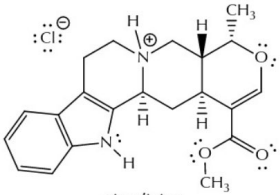
EQ 01.30

On September 23, 2017, the "Google Doodle" honored the 100th birthday of Asima Chatterjee (1917–2006), the first Indian woman to earn a PhD (1944). An organic chemist, one of her contributions was to our understanding of the three-dimensional structure of ajmalicine (below), an antihypertensive drug used to treat high blood pressure.

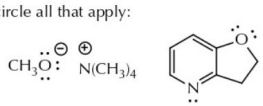
(a) Experimentally, ajmalicine has a pK_a value of 6.31. At the normal pH of the body (physiological pH = 7.40), what will be the major form of ajmalicine in solution?



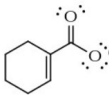
ajmalicine

(b) Which of the following compounds can deprotonate ajmalicine with $K_{EQ} > 10^3$?

circle all that apply:

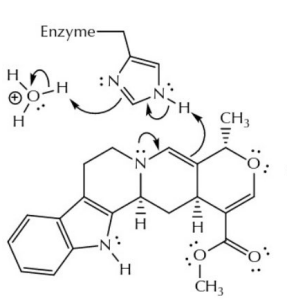


KOH NH_3



LiF Cl_3CH NaSH

(c) The natural origin of ajmalicine is a flower, Indian snakeroot, which is native to the Indian subcontinent and East Asia, and has been used as a traditional herbal medicine for over 2000 years. One critical step in the preparation of ajmalicine in the plant involves a complex protonation reaction that occurs via an enzyme catalyst. Draw the complete result from the following curved arrow mechanism for this step, accounting for all three of the structures. Include the expected three-dimensional orientation of the new CH bond that forms based on the structure of ajmalicine on this page. Follow the representation for how to draw the rest.



Enzyme

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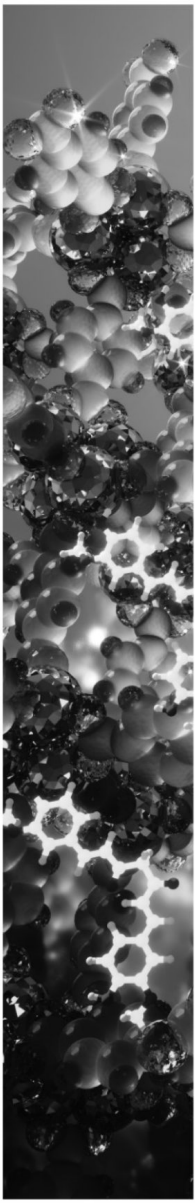

CHAPTER 4

Physical Organic Chemistry: Energetics and Mechanism

Setting the Stage: Writing with Pictures, Drawing with Words

4.1 Classifying Organic Reactions
- A. Complexation-Decomplexation Reactions
- B. Substitution Reactions
- C. Addition Reactions
- D. Elimination Reactions

PRACTICE QUESTIONS

4.2 Diagramming Energy Changes: Mechanisms for Organic Reactions
- A. Complexation-Decomplexation Reactions
- B. Substitution at Hydrogen: Brønsted Acid-Base Reactions
- C. Substitution at Unhindered sp^3 C-X Bonds
- D. General Considerations for Competing and Multistep Reaction Mechanisms

PRACTICE QUESTIONS

4.3 Electrophilic Addition Reactions of Strong Brønsted Acids
- A. Observed Outcomes, Structural Classifications, and Regioselectivity
- B. Proposed Stepwise Mechanism: The Carbocation Intermediate
- C. Relative Stability of Carbocation Intermediates and Their Rates of Formation
- D. Energy Diagram for Electrophilic Addition of Strong Brønsted Acids

PRACTICE QUESTIONS

4.4 Electrophilic Addition Reactions of Weak Brønsted Acids
- A. Observed Outcomes: The Need for a Strong Acid Catalyst
- B. Proposed Stepwise Mechanism: A Catalytic Cycle
- C. Energy Diagram for Electrophilic Addition of Weak Brønsted Acids
- D. Extending Electrophilic Addition to Other Nucleophiles and Electrophiles

PRACTICE QUESTIONS

Reflections About Science: Classification as a Diagnosis Before You Select a Treatment

Summary

CHAPTER QUESTIONS

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CHAPTER 4

Physical Organic Chemistry: Energetics and Mechanism

Setting the Stage: Writing with Pictures, Drawing with Words

Many people compare learning organic chemistry with learning a second language. Their intent is good: they recognize the need for practice and the prevalence of new vocabulary.

But the comparison with learning a second language breaks down. When you learn a second language, you use your native language as an anchor and a point of reference for translation. You already know what numbers are, what colors are, what a chair is, and what it means to run, walk, hop, and sit. The underlying meaning of the new words is familiar, and you learn to associate those new words with things that you already understand. Sure, there are usually new grammatical rules, too; but even then, through defining parts of speech, you tend to make natural comparisons with your native language (a sentence might be structured as noun-object-verb instead of noun-verb-object, and you think in these comparative terms).

Learning organic chemistry is far less like learning a second language, and more similar to learning your first language. The objects (structure and reactivity of organic molecules) are unfamiliar, as are the symbolisms used to represent them (structural drawings, curved arrows), and the words are either new ones (such as "isomer") or familiar ones that have been borrowed and used in new ways (such as "bonding").

Words and drawings interplay with one another, conveying information that is different, and yet which complement one another, to create a complete idea. Instead of saying "a molecule whose structure contains three carbon atoms in a closed ring, each with two hydrogen atoms bonded to them," we draw a triangular shape and understand it to be one of the C_3H_6 structural isomers (*how easily can you visualize that from the words?*). The drawing is a placeholder for a large amount of descriptive information that is conveyed efficiently in its symbolism—and yet, it is literally just three lines drawn as a triangle; you have needed to learn how to associate meaning with this symbol, just as you do with words. And no matter how you arrange the drawings of C_3H_6 structural isomers, the exact terminology "C_3H_6 structural isomers" conveys a specific idea about those molecules that, while present in the drawings, is much more efficiently transmitted through the vocabulary than through a collection of drawings.

Returning to the point: Learning your first language is simply different than learning any second language. Your first language requires fluent experts who can point to the unfamiliar objects and provide the symbols (words), their pronunciation, and their usage. Organic chemistry carries the challenge of having no macroscopic objects to point to, and so the objects (molecules) are imagined and require additional symbolism (drawings) to convey the ideas. Suppose you went back in time, even just a few hundred years, and needed to describe the structure and operation of a cell phone or an automobile. The objects would not exist, and so there is more than a simple translation that you need to accomplish. It's not surprising that terms such as "horseless carriage" and "horsepower" exist, as they build upon existing ideas when confronted with new ones.

This chapter expands the representational forms used to symbolize ideas in organic chemistry. Some of these will be new words, invented to describe ideas for which existing words were inadequate; some of

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these will be familiar words, adopted by organic chemists because they convey something useful for remembering the ideas; and some of these will be graphs and other drawings that capture ideas in an instant, whereas paragraphs of sentences would be needed to convey what is being represented.

As you continue to learn to communicate in organic chemistry, you need to practice using the different symbolic forms (words and pictures) to get at an understanding of the underlying ideas. And while it is easy to fixate on the symbols, they are never the real story. You cannot deduce the characteristics of a cat from the letters "c-a-t" —and in particular, if you have never seen a cat before, and especially if, like molecules, cats had never been observed directly but were proposed to explain other observable phenomena (mysterious purring sounds, gifts of mice on the doorstep).

There is a common saying in the field of semiotics, the study of symbols and their meanings: "The map is not the territory." No matter how detailed the model for something is and no matter how useful it is, the model (our representation for an object) is never the actual object. Virtual reality may seem quite life-like, but it is only a life-like simulation and not the same as actual life. The words and drawings we use to represent organic chemistry are models for our understanding of the underlying existence of molecules and how they operate, but the symbols should not be mistaken for any literal meaning as opposed to what they mean to represent about the imagined world of molecules.

4.1 Classifying Organic Reactions

Organic main group elements form only two types of bonds, sigma and pi. Because chemical reactions involve the interconversions of bonds, and with only two types of bonds in organic structures, the total number of different bond interconversions is quite limited (sigma to sigma, pi to sigma, and so on). The majority of organic chemical reactions can be described by one of, or by a sequence of, a set of only four fundamental reaction classifications that are based upon bond interconversions. In this overview, you may well end up wanting to hear more details than are provided in this chapter. Each of these classifications are worthy of their own books, so pay attention to this introduction as a gross classification process. And although you will soon be able to distinguish between, by way to analogy, a Golden Delicious versus a Granny Smith versus a Honeycrisp apple, we are much more interested at the moment that you can distinguish between an apple, a cookie, and a pizza.

A. Complexation-Decomplexation Reactions

One of the four fundamental reaction categories is the complexation-decomplexation reaction (see Sections 1.4B and 3.1C), involving open shell atoms and their reactivity. From a bond interconversion perspective, the complexation-decomplexation reaction is the formation of a sigma bond starting with no bond (complexation), or the reverse process (decomplexation) where a sigma bond is broken heterolytically and one of the two previously bonded atoms ends up with the pair of electrons from the broken bond.

According to the generalization used in this text (Section 3.2C), the complexation-decomplexation reaction is synonymous with a Lewis acid-base reaction, where a new bond forms when an electron pair donor (Lewis base) shares its electron pair with an open shell atom (Lewis acid). A few more examples of this reaction are shown in Figure 0401. Historically, different verbs have been used to describe this bonding change. A cationic open shell atom is "captured" by the Lewis base. A sigma bond that breaks to give at least one ion is "ionized" or has undergone "ionization." In other cases, where the bond-breaking step is favorable, the sigma bond "dissociates" or has undergone "dissociation." As is true about language, in general, any preferred usage of these different terms is mainly dictated by custom rather

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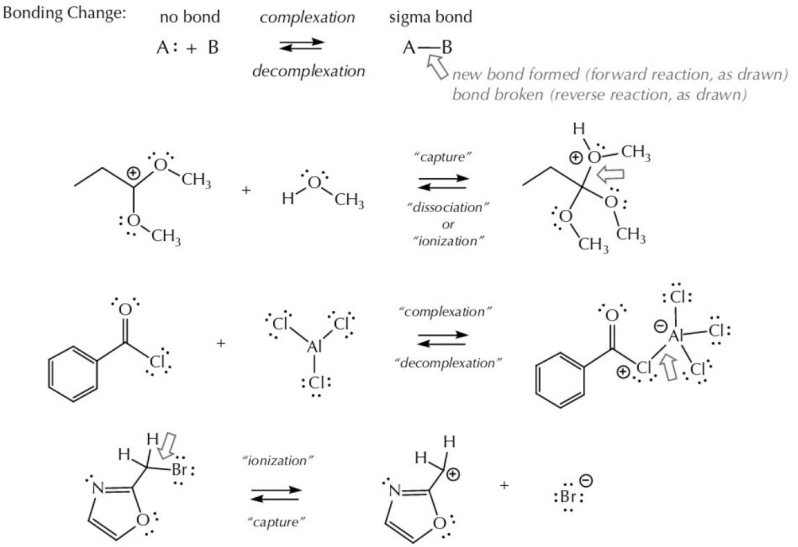
than any definable rules. More commonly, the linguistic variation is merely a way to give writers or speakers synonyms that can keep descriptions from becoming too redundant. At this point, worry less about what specific word might be used and when, and more on recognizing that a family of synonyms exists for the bond forming process (complexation, capture) relative to the bond breaking process (de-complexation, dissociation, ionization).

Figure 0401
Representative complexation-decomplexation reactions.



B. Substitution Reactions

The exchange of one sigma bond for another is called a substitution reaction. Brønsted acid-base reactions are all examples of substitution reactions, as the sigma bond involving a hydrogen atom, the Brønsted acid, is broken and replaced to form the conjugate acid. Accordingly, Brønsted acid-base reactions are also referred to as "substitution reactions at hydrogen," as the new and old sigma bonds have been formed and broken with respect to the hydrogen atom. In General Chemistry, you may have encountered "dis-placement reactions" and "replacement reactions" as synonyms for substitution reactions.

Specific organic reaction mechanisms are often abbreviated, and substitution reactions are identified by a capital "S" (for Substitution). As illustrated in Figure 0402, (on the next page) substitution reactions can involve a diverse array of atoms, and yet the fundamental sigma-to-sigma change unifies these examples as a reaction classification. The reverse of a substitution reaction is also a substitution reac-tion, as the sigma-to-sigma bond change is the same in both directions. Substitution reactions can happen intramolecularly (within the same molecule), which results in the formation of a new ring.

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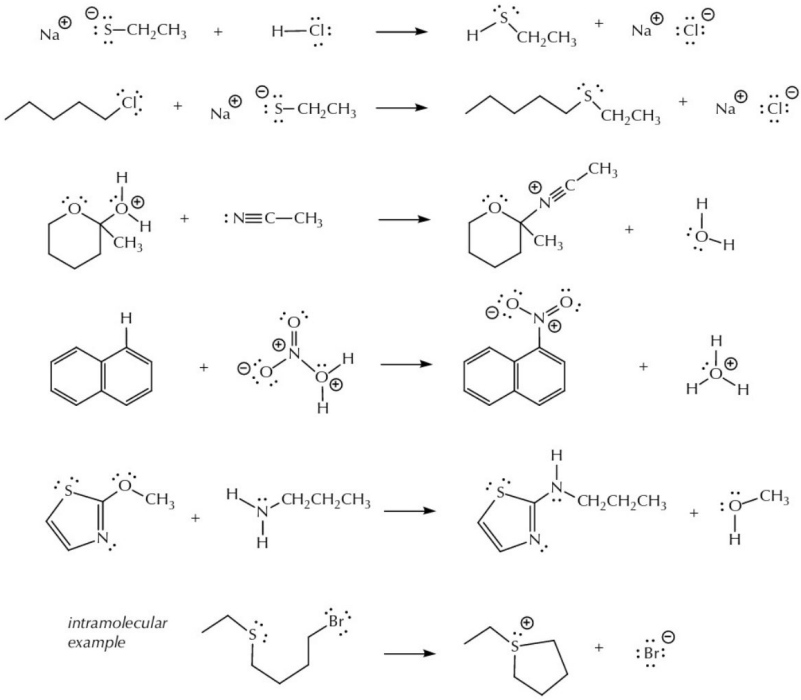
Figure 0402

Examples of substitution (S) reactions.

Reaction Classification: Substitution (S)

Bonding Change: sigma bond A—B C $\rightleftharpoons$ *substitution* *substitution* sigma bond A B—C



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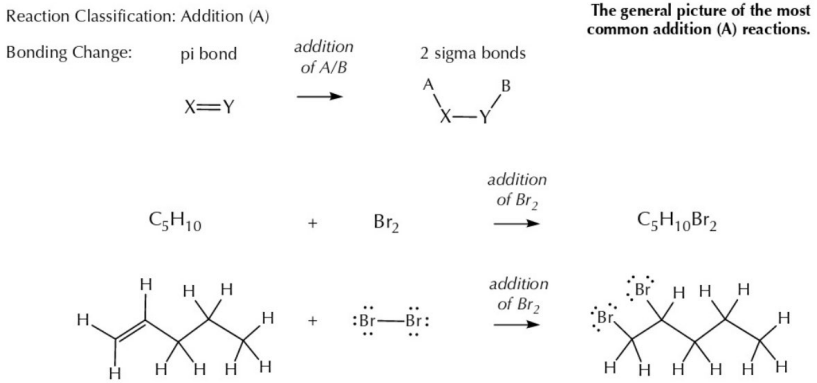
C. Addition Reactions

As introduced in Section 1.3C, the third classification of organic chemical reactions is addition, identified by a capital "A" in mechanistic abbreviations. Historically, the word "addition" referred to the arithmetic of all the atoms from two reagents adding together to give a single product (e.g., $C_5H_{10} + Br_2$ -> $C_5H_{10}Br_2$). In General Chemistry, you may have encountered the same arithmetic concept as a "combination reaction" (e.g., 2 Na + Cl_2 -> 2 NaCl).

From a bonding perspective, most addition reactions are represented by breaking a pi bond and forming a new sigma bond at each of the two atoms that were involved in the pi bond (Figure 0403). As with substitution reactions, there are different mechanisms for addition reactions that depend on the particular reagents involved and the timing of the steps, but the overall structural result from an addition is a defined category.

Figure 0403
The general picture of the most common addition (A) reactions.



With small and simple molecules (Br_2, H_2, H_2O), it is easy to predict the result from an addition reaction, provided you are told that it is an addition, because all of the atoms need to be incorporated into the final product. Triple bonds are built from two pi bonds, and each of them can undergo addition; thus, triple bonds can undergo addition by one or two equivalents of a reagent, and the information about the ratio of the reactions must be provided explicitly. Sometimes an addition reaction takes place with a reagent that does not break apart when the two new sigma bonds form, and a ring of atoms results. Addition reactions that form rings are called cycloaddition reactions. Although less commonly encountered in the introductory course, some sigma bonds can also be broken and undergo an addition reaction by some of these same reagents under the right conditions.

Linguistically, we say that the pi bond has been "added to" by the reagent with which it combines. In the earlier example ($C_5H_{10} + Br_2$ -> $C_5H_{10}Br_2$), we would say "molecular bromine (Br_2) has added to the C_5H_{10} molecule." We might also phrase it as "C_5H_{10} has undergone an addition of bromine." The specific label for an addition reaction derives from the reagent that is adding. The "addition of molecular bromine" is called "bromination." Addition of hydrobromic acid (HBr) is called "hydrobromination," the addition of water is "hydration," and the addition of hydrogen is "hydrogenation." A triple bond might undergo "bromination" (addition of one equivalent of bromine) or "double bromination" (the addition of two equivalents of bromine).

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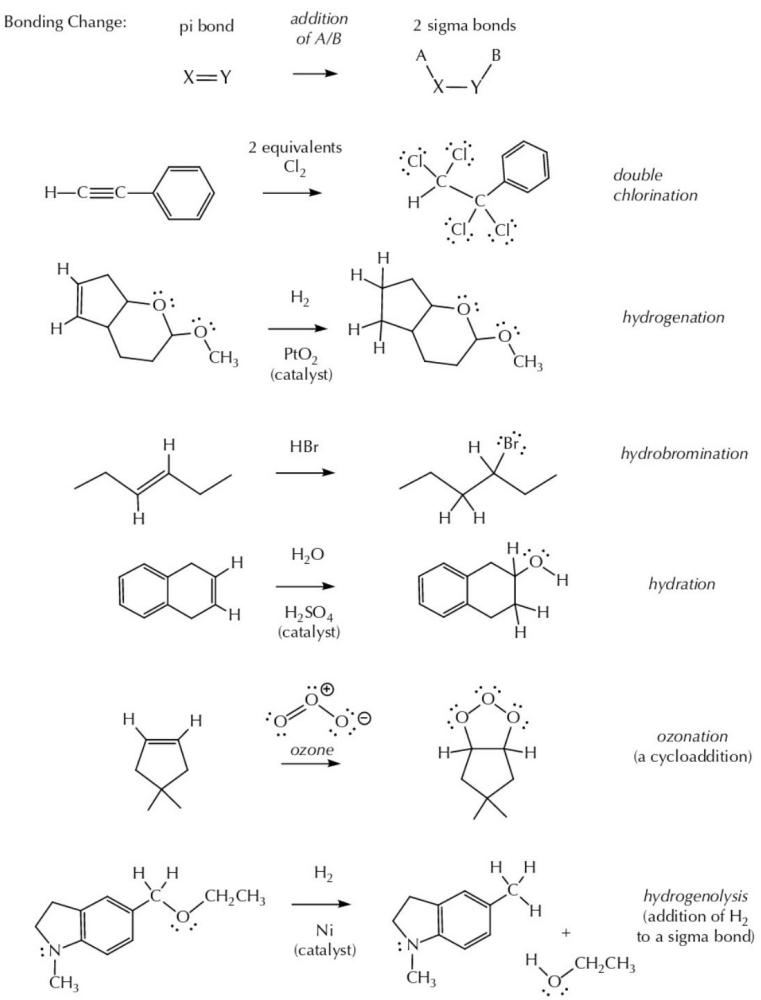
Figure 0404

Examples of addition (A) reactions, including cycloaddition reactions.



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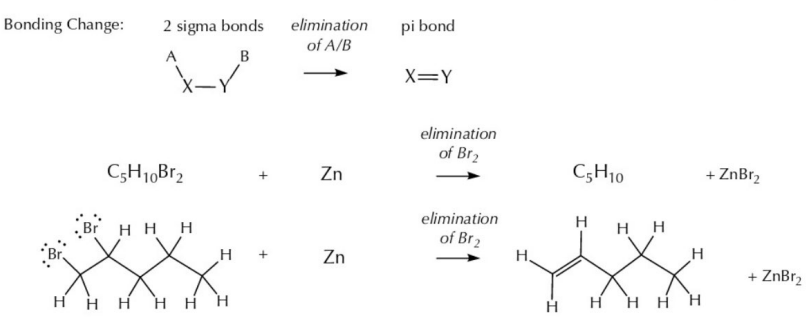
A variety of different addition reactions, and their labels, are shown in Figure 0404. In the last example in this list, a sigma bond adds hydrogen (the sigma bond brakes, and a hydrogen atom is added to the two atoms that were previously bonded), and so the process is called "hydrogenolysis" (to break with hydrogen) rather than hydrogenation. You will see here that the categorical label for a reaction is sometimes driven by its common usage rather than a strict definition. Hydrogenolysis quite rightly belongs with the substitution reactions if you examine the bonding changes (a sigma-to-sigma change). However, there is a historical association with common reagents, such as molecular hydrogen, that were already observed participating in addition reactions of double and triple bonds, and this has resulted in a crossover in the way the terms are used. These uses are linguistic customs that you will pick up over time.

Addition is the name of the forward reaction only, where a pi bond (typically) has been broken and two new sigma bonds have formed; the reverse reaction of addition is its own category, called elimination, which is the final fundamental reaction type, and described in the next section.

Figure 0405
The general picture of elimination (E) reactions.



D. Elimination Reactions

Elimination reactions ("E") are the reverse of addition reactions. In the most commonly encountered cases, two sigma bonds on adjacent atoms are broken and replaced by a new pi bond between these two adjacent atoms (Figure 0405). Linguistically, specific elimination reactions use labels that explicitly acknowledge them as the reverse of addition reactions. Elimination reactions are usually labeled using the "de-addition" construction of the specifically named process. For example, the two bromine atoms from $C_5H_{10}Br_2$ can be removed with zinc metal to give the original C_5H_{10} molecule, plus zinc dibromide ($ZnBr_2$): $C_5H_{10}Br_2 + Zn \rightarrow C_5H_{10} + ZnBr_2$. The loss of bromine in this elimination reaction is called "debromination." Note that the elimination reaction is defined with respect to the organic molecule, and molecular bromine (Br_2), the reagent used in the addition, is not being regenerated.

The elimination of HBr is "dehydrobromination," the elimination of water is "dehydration," and the elimination of hydrogen is "dehydrogenation." The reverse of a cycloaddition reaction is called a "cyclore-

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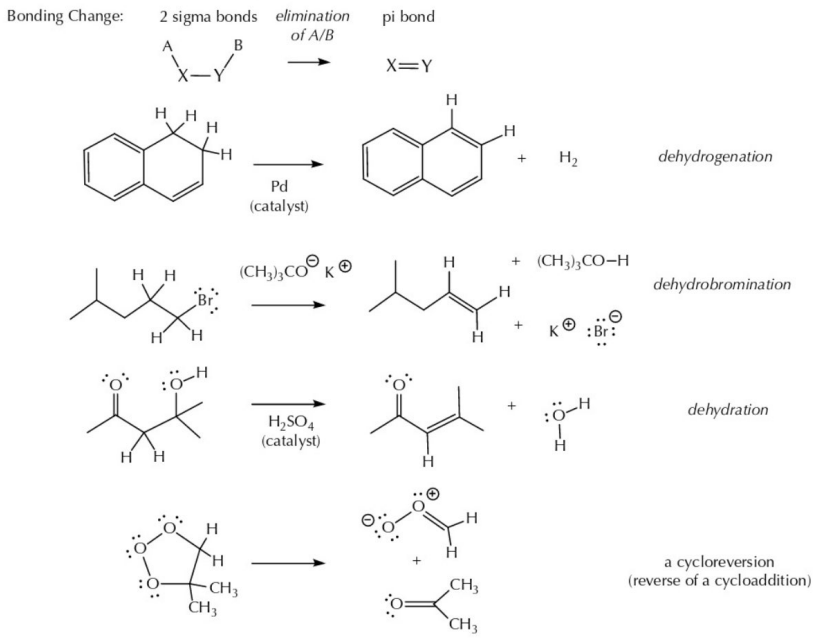
version reaction" as a synonym for an elimination reaction. A variety of different elimination reactions, and their labels, are shown in Figure 0406.

You might be eager to have the details for how these reactions take place. Relax; we will get there. For now, we are playing a game of "animal, vegetable, or mineral," making gross classifications that can take millions of examples of different-looking reactions and drop them into one of four categories. This process is the beginning of mechanistic classification, which will allow you to take a few general concepts and apply them broadly to new and unfamiliar examples. In this first set of practice questions, you will begin to see how powerful the general ideas of organic chemistry can be in allowing you to read and understand something about reactions, even though you have never encountered them before.

Figure 0406

Examples of elimination (E) reactions.



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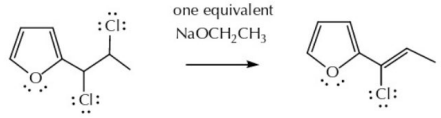
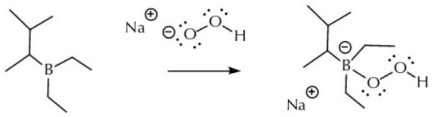
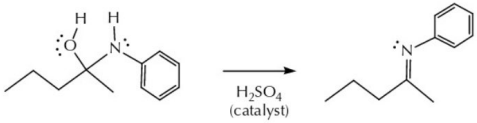
PRACTICE QUESTIONS

4.01 Classify each of the following transformations according to one of the four fundamental types of reactions: complexation-decomplexation, substitution, addition, or elimination. For the addition and elimination reactions, provide the more specific classification (e.g., bromination, dehydration) based upon the given information.

(a)


(b)


(c)


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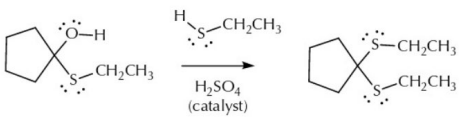

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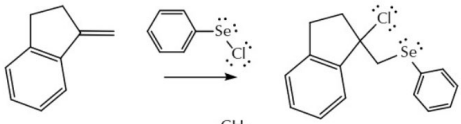
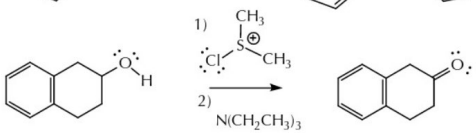
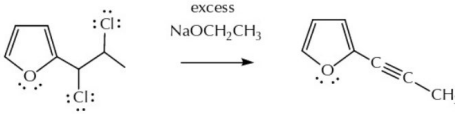
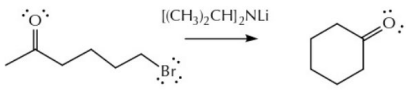


(f)


(g)


(h)


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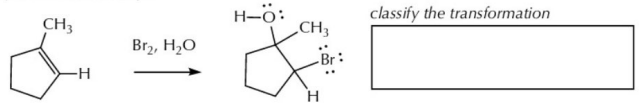
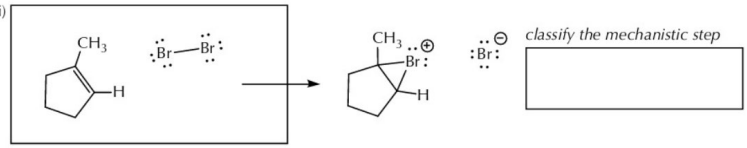
4.02 For each of the following transformations, classify the overall transformation according to one of the four fundamental types of reactions: complexation-decomplexation, substitution, addition, or elimination. These reactions occur by multistep mechanisms. Provide the curved arrow notation for each of the steps, and also classify the individual steps.

(a)



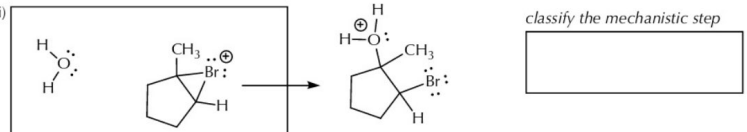
classify the transformation

(i)



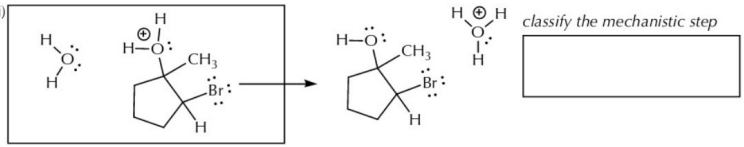
classify the mechanistic step

(ii)



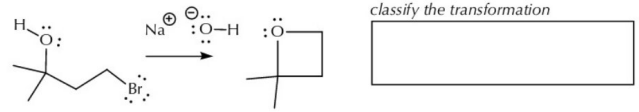
classify the mechanistic step

(iii)



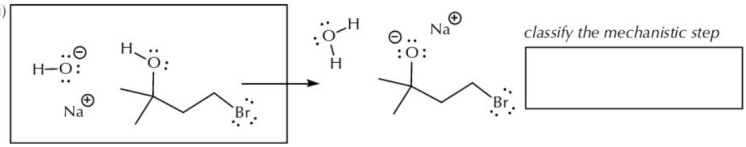
classify the mechanistic step

(b)



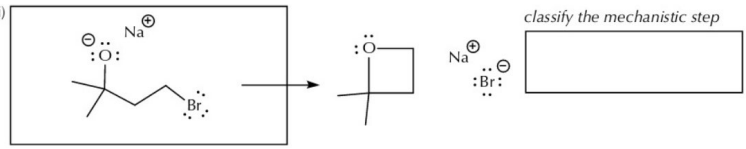
classify the transformation

(i)



classify the mechanistic step

(ii)



classify the mechanistic step

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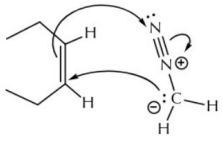
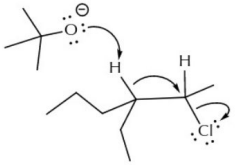
4.03 The following transformations are proposed to take place in one mechanistic step. Provide the products, in balanced equations, that are implied by the curved arrows, and classify the overall transformation according to one of the four fundamental types of reactions: complexation-decomplexation, substitution, addition, or elimination.

(a)



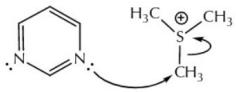
classify the transformation

(b)



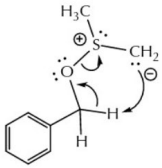
classify the transformation

(c)



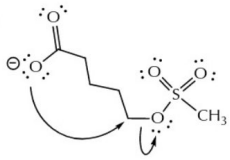
classify the transformation

(d)



classify the transformation

(e)



classify the transformation

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4.2 Diagramming Energy Changes: Mechanisms for Organic Reactions

The subfields of chemistry overlap. Organic chemistry was originally called "organical chemistry," meaning related to the body and its organs, and in the 1830s became the part of chemistry concerned with molecules, built from the main group elements, occurring in the compounds that make up and/or interact with biological organisms. Both biological and nonbiological organic compounds with important material properties are found in the area of polymer chemistry, providing your body with hair, skin, and muscles, as well as with the abundance synthetic materials (plastics) that we use every day.

Physical chemistry is a subfield with a substantial overlap between chemistry and physics. Physical chemistry involves understanding the relative energy and transfer of energy that takes place in reactions (thermodynamics), and the relative rates for chemical phenomena (kinetics). It also includes developing theoretical models for understanding relative stabilities, relative rates, and spectroscopy, the interaction of electromagnetic radiation (e.g., visible light, microwaves, radio waves, infrared and ultraviolet radiation) with molecules, all collectively covered by an area called quantum mechanics.

Physical organic chemistry is a field that grew into existence during the 1950s and 1960s, as chemists carried out physical chemistry experiments to better understand the fundamental mechanistic model for organic chemical reactions. The study of reaction mechanisms derives from physical organic chemistry. These mechanisms can be expressed with curved arrows, with mathematics, and with graphs and diagrams used to represent the energy changes that take place during a reaction. Physical organic chemistry explains how and why some reactions take place, why others do not, and why some are more or less favorable than others.

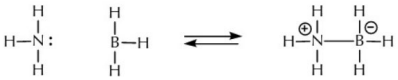
The remainder of this chapter looks into the mechanistic detail, as revealed by physical organic chemistry, for some of the fundamental reactions whose classifications were introduced in Section 4.1.

A. Complexation-Decomplexation Reactions

The complexation-decomplexation (Lewis acid-base) reaction is one of the most fundamentally simple chemical reactions: a bond forms (complexation) or a bond breaks (decomplexation), using a Lewis acid-base change, that is, the sharing or loss of an electron pair (rather than the combination of two individual unpaired electrons). The reaction between ammonia (NH_3) and borane (BH_3) is an example of this process (Figure 0407). Because the complexation product, with its boron-nitrogen bond, provides all closed shell atoms, we have previously stated that the right-hand side of this equation would be favorable. The ammonia-borane complex is more stable than the two isolated reactants, ammonia and borane, and the equilibrium constant for the process, as shown, would be much greater than 1.

Figure 0407

Complexation-Decomplexation Reaction Between Ammonia and Borane.



An energy diagram can be used to represent the ideas described by text, above. Typically, these are two-dimensional graphs where the y-axis (vertical) designates relative energy as a measure of stability. Lower energy means more stable. The usual designation "E" (for energy) is intentionally ambiguous. A more rigorous study of physical chemistry would define the energy in terms of enthalpy and/or entropy. For the purposes of descriptive organic chemistry, we are using energy as a stand-in term for relative stability, as

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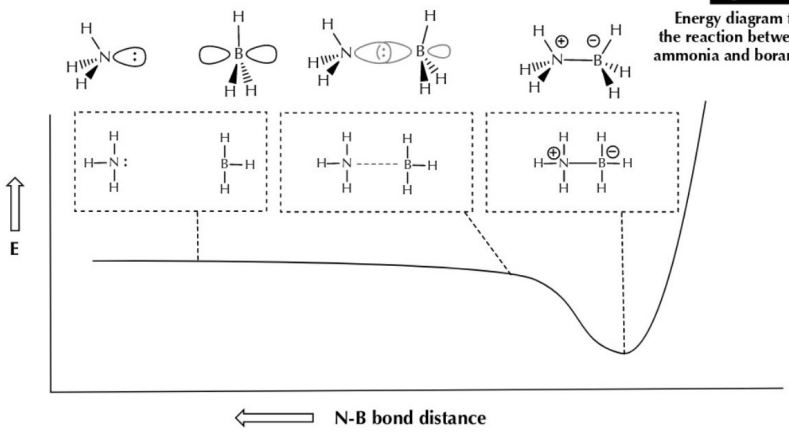
a way to rank and then show what is more stable and what is less stable. Along the x-axis (horizontal) is typically a distance (how close a set of reagents are in space) or a time dimension (how much progress there has been moving from left to right, or right to left, in the represented chemical reaction).

An energy diagram for forming and breaking of the nitrogen-boron bond in the reaction of ammonia with borane is shown in Figure 0408. Reading the diagram from left to right, the distance decreases as the nitrogen and boron atoms come together. Starting on the left, the ammonia and borane molecules are separated by some distance and they are too far apart for the nitrogen and boron atoms to be interacting, so this constitutes the energy baseline (no bonding). As the ammonia and borane molecules get closer, along a trajectory that brings the nitrogen and boron atoms together, the electron pair from the nitrogen can begin to be shared with the open shell (empty p orbital) of the boron atom. Along this trajectory, a favorable orientation of the two molecules is implied; that is, the nitrogen atom is headed directly towards the open shell boron atom and is not about to collide with one of the hydrogen atoms in borane (and bounce off…every collision does not result in a reaction). The energy diagram in Figure 0408 illustrates a productive collision (i.e., produces a chemical outcome) and not one of the many nonproductive collisions that might take place.

Figure 0408
Energy diagram for the reaction between ammonia and borane.



Along this favorable bond-forming trajectory, the sharing of the nitrogen atom's electron pair starts to close the shell around the boron atom and the overall combination of the two molecules is more stable than when they were separated from one another. At some point, the nitrogen and boron atoms are sitting at the optimal bonding distance (the energy minimum), where the electron pair is being shared (closed shell configuration for both atoms, and the electrons are attracted to both nuclei) and where the nuclear-electron attraction is being balanced out by the repulsion of the two positively charged nuclei. Also depicted: What happens if the two molecules get closer and the bond shortens? If the distance between the nitrogen and boron atoms continues to decrease, the same-charge repulsion between the nuclei would increase exponentially, causing the stability to decrease.

Each point along the curve represents the relative energy of an actual molecular structure, where the atoms have specified bond distances, geometry, and charge. An energy diagram can also be read from right to left, which in this case represents the bond breaking process. Notice that neither of the axes

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includes a scale or units. In organic chemistry, these diagrams are often used to represent qualitative relationships (more or less stable, longer or shorter distance) rather than quantitative ones (although they can certainly be combined with the results from mathematical calculations or actual experiments).

B. Substitution at Hydrogen: Brønsted Acid-Base Reactions

In Brønsted acid-base (substitution at hydrogen) reactions, two bonding changes are involved. For example, in the reaction between ammonia and hydrobromic acid (Figure 0409), an HBr sigma bond is broken and a new NH sigma bond is formed.

Figure 0409

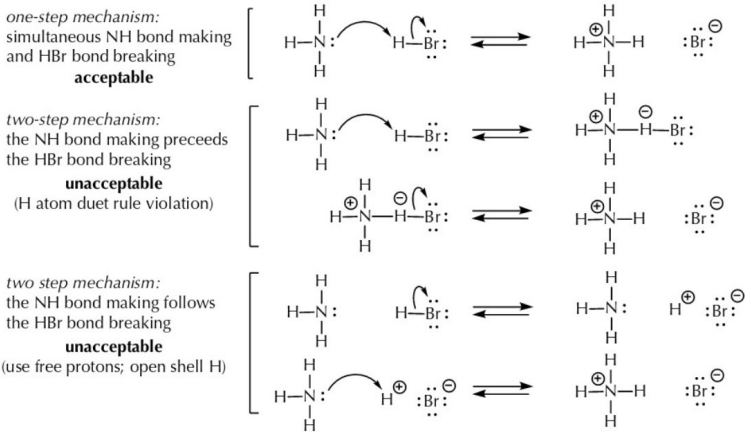
The reaction between ammonia and hydrobromic acid.

Based on the study of acid-base chemistry in Chapter 3, you already know that the acid-base reaction, as drawn here, lies to the right, and with a relatively large K_{EQ}, given the difference of 17 in the pK_a values. From Section 3.2B, we have assumed that the mechanism of the reaction involves the two bond changes occurring simultaneously, and so we showed both of the curved arrows at the same time.

The timing of the bond-change events is critical to what we mean by the mechanism of any reaction, and there are two other options, at least in theory, that should be considered in addition to simultaneous bond breaking and formation: (1) that the bond-forming event precedes the bond-breaking event, and (2) that the bond-breaking event precedes the bond-forming event. How these three options would be depicted using the curved arrow notation is shown in Figure 0410. If the bond-forming event happens first, then

Figure 0410

Three mechanistic options for the reaction between ammonia and HBr.


one-step mechanism:
simultaneous NH bond making and HBr bond breaking
acceptable
two-step mechanism:
the NH bond making preceeds the HBr bond breaking
unacceptable
(H atom duet rule violation)
two step mechanism:
the NH bond making follows the HBr bond breaking
unacceptable
(use free protons; open shell H)

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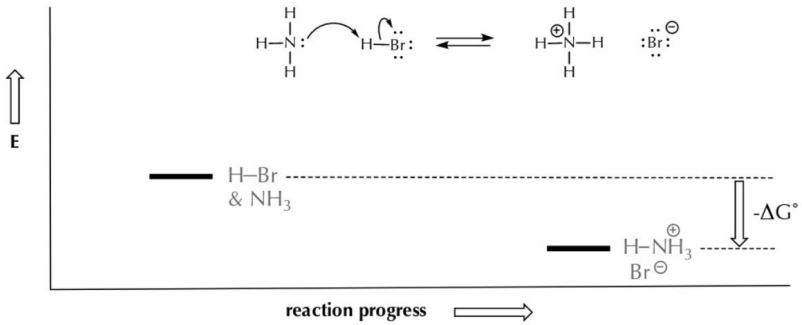
there is a violation of the duet rule, exceeding the closed shell electron configuration of a hydrogen atom. This is impossible (or, at least, it should not be proposed without a great deal of supporting evidence). If the bond-breaking event happens first, then a free, open shell proton is proposed, and this is not favorable, either (Section 3.2C). The best option is the simultaneous events because none of the atoms ever needs to be open shell, and none of them violates the closed shell limit, either.

The story told by the drawings and the curved arrows needs to be the same one that an energy diagram tells. An energy diagram for this reaction, then, needs to show the HBr bond breaking at the same time the NH bond is forming, in the same, single mechanistic step, along with representing the relative stabilities that are implied by the pK_a values (the NH bond is more stable than the HBr bond). Figures 0411–0413 illustrate the development of this energy diagram.

In Figure 0411, the relative stability of the two bonds is designated. Reading from left to right, the less stable HBr sigma bond becomes the more stable HN sigma bond (reminder: the relative stability is inferred from the difference in the pK_a values, which indicate the direction of the reaction: the weaker acid represents a more stable bond, which is lower in energy and harder to break). The horizontal x-axis is referred to as the "reaction coordinate" and represents the progress of the reaction as it occurs. Also reading from left to right, the difference in energy between the starting point and the ending point is downhill, or a negative value, and customarily represented as $-\Delta G^\circ$ ("a negative delta-G zero"). Although the energy scale has not been defined, this reference to ΔG° (the standard free energy difference) is used as an inexact convention.

Figure 0411

Developing an energy diagram: placement of reactants by relative stability.



Recall from General Chemistry that ΔG° values and equilibrium constants (K_{EQ}) have an exact mathematical relationship ($\Delta G^\circ = -RT\ln K_{EQ}$). These energy diagrams provide a nice visualization of this relationship, and in a way that makes intuitive sense. Reading from left to right, if the ΔG° is negative, then the products are more stable, and the K_{EQ} is greater than 1, which is consistent with the right-hand term of the equation being negative. If the ΔG° is zero, then the products are the same energy as the reactants, and the K_{EQ} is equal to 1 (and the $\ln(1) = 0$, so that right hand term is, indeed, 0). And if the ΔG° is positive, and the products are less stable than the reactants, the K_{EQ} is less than 1 (the log of a fraction is a negative number, and the right-hand term is positive). As ΔG° pivots around a value of zero (negative/zero/positive), the K_{EQ} pivots around a value of one (fraction/one/greater than one).

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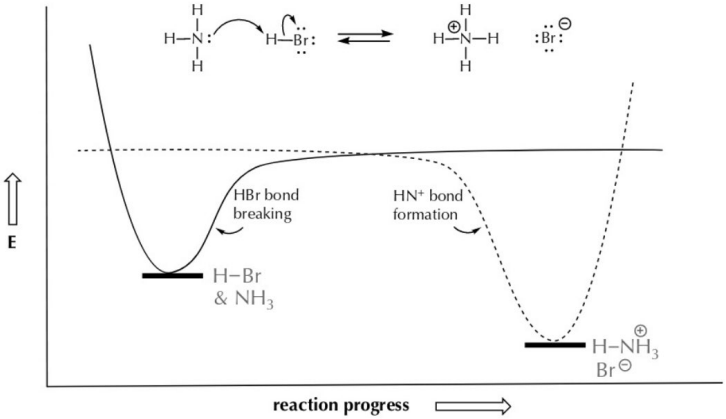
In Figure 0412, the two bond-change events are shown independently: breaking the HBr bond (solid line) is shown separately from the formation of the HN bond (dashed line), using the same bond forming and breaking energy curves that were used in Figure 0408, according to the direction of its forming or breaking.

Figure 0412

Developing an energy diagram: individual bond-change events.



And in Figure 0413, the two independent energy curves are combined, as required by the two bond-change events happening at the same time. This is a typical representation for substitution reaction where the two bond-change events occur simultaneously. Every point on the energy curve is a structure built from all of the atoms. Of particular note is the structure at the energy maximum, sitting between the starting materials and the products, called the transition state structure.

Figure 0413

Developing an energy diagram: an integrated picture.

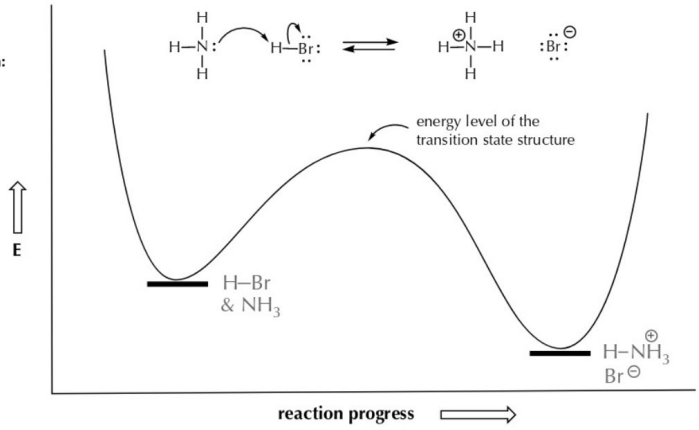


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Figure 0414 presents the imagined transition state structure for this Brønsted acid-base reaction. Of note: (1) The 180° (linear) relationship of the N-H-Br set of atoms is intentional, as we imagine the collision of the nitrogen atom to be most effective along the HBr bond axis, and from the exact opposite side as the bromine atom. This is customarily called the "billiard ball model" for the collision, as it is a direct analogy to how one might strike one of a pair of balls, with a third, to get the most efficient transfer of energy and motion (see "Setting the Stage," Chapter 3). (2) The dotted lines represent partial bonds, so these are unequally shared electron pairs that keep an average number of two electrons associated with the hydrogen atom as the HBr bond is breaking and the new NH bond is forming. Of note: The dotted lines are the shared electrons, not a representation of a force, and so no nonbonding electron pairs are shown at the atoms where these bonds are forming and breaking. (3) By convention, the atoms where a formal charge is changing will hold a partial charge that is in between the starting and ending charges. That is: The nitrogen starts off uncharged and ends up as +1, so it is partially positive in the transition state structure. The hydrogen atom is uncharged both before and after, and so it is uncharged in the transition state structure. The bromine atom starts off uncharged and ends as -1, so it is partially negative in the transition state structure.

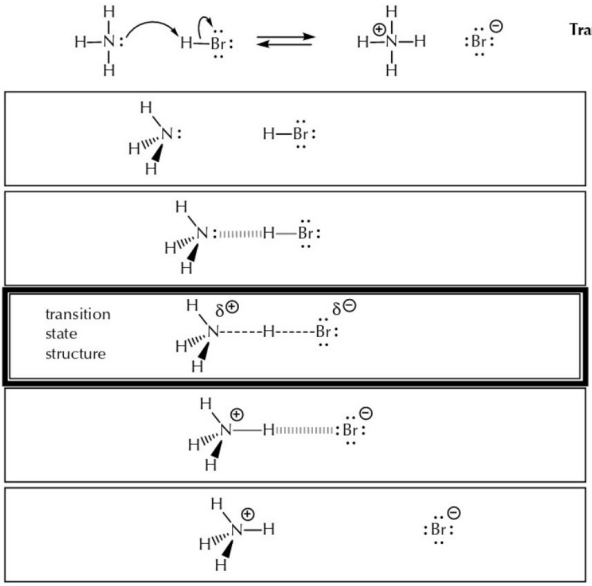

Figure 0414
Transition state structure.

As stated earlier, every collision does not result in a reaction. Sometimes the molecules collide with the wrong trajectory, and they simply bounce off one another. Sometimes they do not have enough energy to cause the reaction to take place, that is, to achieve the high-energy transition state structure, and so they, once again, just bounce off one another. Under normal conditions of temperature and concentration, molecules in solution collide about 10^8 to 10^9 times per second. Brønsted acid-base reactions are some of the fastest reactions known. A favorable proton transfer reaction takes place at about 10^7 times per second, meaning that one in every 10–100 collisions results in a reaction. Most reactions take place more slowly than this, as the collisions require more energy and/or a more specific trajectory.

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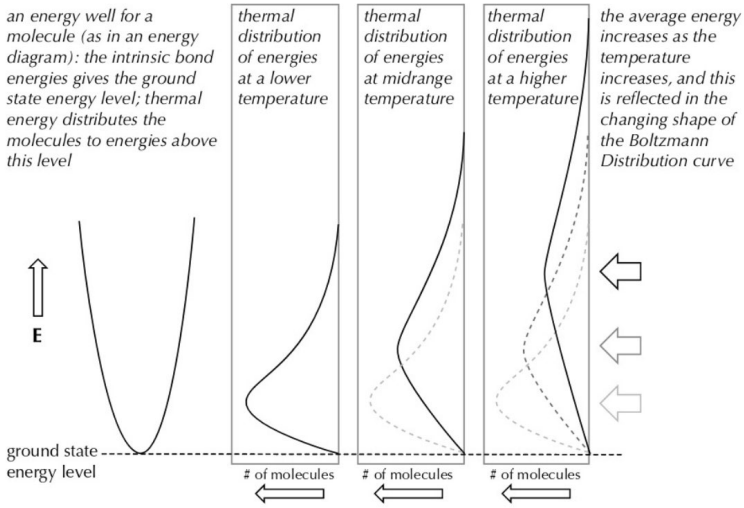
The low energy points on the energy diagrams are called the ground state energies. These are the intrinsic stabilities of the structures relative to a bunch of unbounded atoms. None of the molecules are actually at this energy level, however, because of another reality: Chemistry is not taking place at absolute zero. At any temperature above absolute zero, molecules are vibrating, rotating, and moving about, colliding with one another as they exchange thermal energy with their environment. And in a typical chemical reaction, there are many (many!) molecules present. Recall that one cubic centimeter of water has 10^{23} water molecules in it, and thanks to the thermal energy of motion, they are distributed over a wide range of total energies. And as the temperature increases, and motion and collisions increase, the range of energies gets broader. This distribution of energies is represented in Figure 0415. As the temperature increases, the range of energy values for the molecules increases. This range is called the Boltzmann Distribution.

Figure 0415

The Boltzmann Distribution of molecular energies at different temperatures.


an energy well for a molecule (as in an energy diagram): the intrinsic bond energies gives the ground state energy level; thermal energy distributes the molecules to energies above this level
thermal distribution of energies at a lower temperature
thermal distribution of energies at midrange temperature
thermal distribution of energies at a higher temperature
the average energy increases as the temperature increases, and this is reflected in the changing shape of the Boltzmann Distribution curve
E
ground state energy level
# of molecules
# of molecules
# of molecules

The concept of a large numbers of molecules with a Boltzmann Distribution of energies combines meaningfully with an energy diagram. When you look at the spot where the starting materials are located on the curve of an energy diagram, it is tempting to interpret it as all of the molecules of ammonia and borane just sitting (energetically) at the bottom of the valley. This is not true. Above absolute zero (and room temperature, around 20°C, is about 300 K) the molecules experience significant thermal motions, and they are energetically distributed upwardly, dictated by the temperature of the system and according to the Boltzmann Distribution (Figure 0416).

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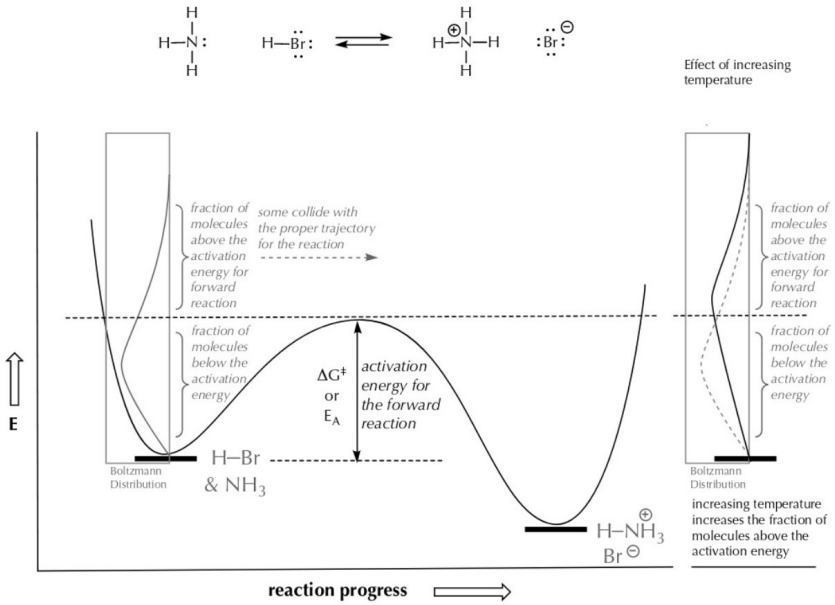
The distance from the ground state energy to the transition state energy is called the Energy of Activation (E_A) or $\Delta G^{\ddagger}$. Only molecules at that energy level (or above), and then only the fraction with the right trajectory for the collision, will proceed from left to right and undergo the reaction. The higher the energy of activation, the fewer molecules there are above that level, and the slower the reaction.

Figure 0416

Energy of activation versus Boltzmann Distribution.


Effect of increasing temperature
fraction of molecules above the activation energy for forward reaction
some collide with the proper trajectory for the reaction
fraction of molecules below the activation energy
ΔG‡ or E_A
activation energy for the forward reaction
E
H–Br & NH3
Boltzmann Distribution
H–NH3 Br
reaction progress
increasing temperature increases the fraction of molecules above the activation energy

As you increase the temperature, the distribution of molecular energies shifts upwards (Figure 0415). And as illustrated on the right-hand side of Figure 0416, the upwards shift in the distribution means that more molecules are above the energy of activation, and more can react, and so the reaction goes faster; that is, more molecules per second are transformed from starting materials to products.

The situation of the products' side of the diagram mirrors that of the starting materials. Energetically, the product molecules are not sitting at the bottom of the energy well but are also arrayed at exactly the same thermal distribution at the starting material, also according to the Boltzmann Distribution. In this diagram, where the products are more stable than the reactants, the energy of activation for the reverse reaction is higher than for the forward reaction, and at any given temperature, the fraction of molecules above that higher activation energy will be lower than for the forward reaction (Figure 0417).

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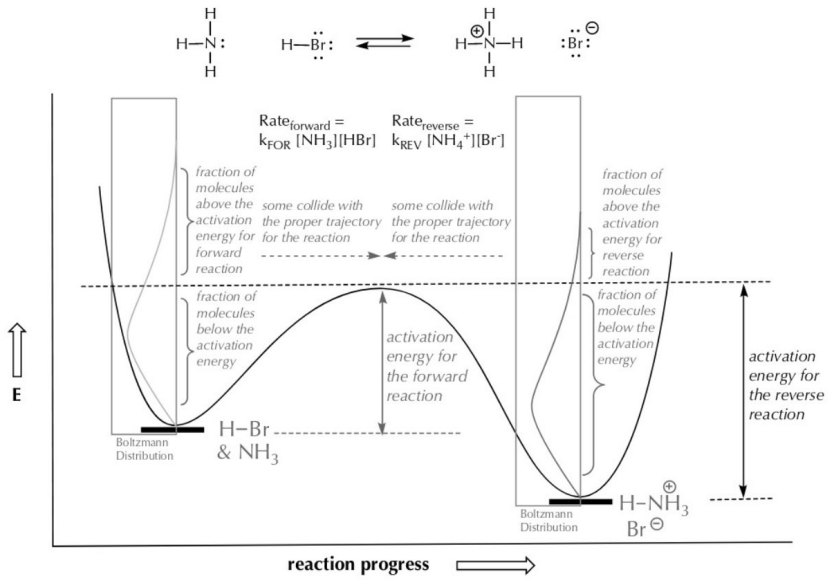
Figure 0417

Equilibrium is defined by the rates of the forward and reverse reactions.


Rate$_{forward}$ = k_{FOR} [NH_3][HBr]
Rate$_{reverse}$ = k_{REV} [NH_4^+][Br^-]
fraction of molecules above the activation energy for forward reaction
some collide with the proper trajectory for the reaction
some collide with the proper trajectory for the reaction
fraction of molecules above the activation energy for reverse reaction
fraction of molecules below the activation energy
activation energy for the forward reaction
fraction of molecules below the activation energy
activation energy for the reverse reaction
E
Boltzmann Distribution
H–Br & NH_3
Boltzmann Distribution
H–NH_3^+ Br^-
reaction progress

the products are more stable than the starting materials:

$\Delta G^\circ < 0$

$K_{EQ} > 1$: concentration of NH_4^+ Br^- is greater than NH_3 + HBr at equilibrium

$E_{A(forward)} < E_{A(reverse)}$

$k_{FOR} > k_{REV}$

the relationship between equilibrium and reaction rates

equilibrium: Rate$_{forward}$ = Rate$_{reverse}$

$k_{for}[NH_3][HBr] = k_{rev}[NH_4^+][Br^-]$

$$K_{EQ} = \frac{[NH_4^+][Br^-]}{[NH_3][HBr]} = \frac{k_{for}}{k_{rev}} > 1$$

A set of relationships that can be read from the energy diagram are shown at the bottom of Figure 0417. These three relationships are synonymous with the products being more stable than the starting materials:

(a) $\Delta G^\circ < 0$ (an exergonic reaction)
(b) the equilibrium constant is > 1 (concentration of products > starting materials at equilibrium)
(c) the energy of activation for the forward reaction < the energy of activation for the reverse

Reaction rates are also related to the relationships among these quantities. Reaction rates are dictated by the concentration of the reacting partners in combination with a variety of factors that are lumped together as the rate constant (k). In this Brønsted acid-base example, the rate of the forward reaction is $RATE_{FORWARD} = k_{FOR}[NH_3][HBr]$, while the rate of the reverse reaction is $RATE_{REVERSE} = k_{REV}[NH_4^+][Br^-]$. The rate constants take the energies of activation into account, as well as temperature and the fraction of molecules with the proper trajectory.

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Energy diagrams also allow us to read the relationships within the concept of equilibrium, which is defined as when the rate of the forward reaction equals the rate of the reverse. Looking at the rate equations, that means that equilibrium is defined by $k_{FOR}([NH_3][HBr]) = k_{REV}([NH_4^+][Br^-])$, or, after a little algebra: $K_{EQ} = ([NH_4^+][Br^-])/([NH_3][HBr]) = k_{FOR} / k_{REV}$.

According to the energy diagram, the two ratios at the end of the previous sentence make qualitative sense:

(1) as drawn in the diagram, $K_{EQ} > 1$ because the products are more stable than the reactants;
(2) because the products are more stable, there are more of them: $([NH_4^+][Br^-])/([NH_3][HBr]) > 1$;
(3) the energy of activation for the forward step is lower than for the reverse, and so the forward reaction should be faster than the reverse reaction; that is, the rate constant for the forward reaction is higher in value: $k_{FOR}/ k_{REV} > 1$.

Thus, the larger rate constant ($k_{FOR} > k_{REV}$) is coupled with the reactants, whose concentration is lower than the products ($[NH_3][HBr] < ([NH_4^+][Br^-])$, making it reasonable to expect that, at some point $k_{FOR}([NH_3][HBr])$ can be equal to $k_{REV}([NH_4^+][Br^-])$, which define equilibrium (the rates of the forward and reverse reactions are equal).

C. Substitution at Unhindered sp^3 C-X Bonds

The common hydrohalic acids (HCl, HBr, HI) are all relatively strong Brønsted acids with low pK_a values. These three H-X bonds (X=halogen), in other words, all participate quite predictably in substitution reactions (i.e., Brønsted acid-base, proton transfer reactions). By analogy, bonds between other atoms and the halogen atoms are observed to undergo substitution reactions; not all types, but some. Although the details for these reactions will be presented in later chapters, one brief introduction to reasoning by analogy is presented here as an example of how the reactivity seen in one type of bond can extend to another.

The molecules on which this analogy is built are: (a) hydrocarbons where an sp^3 C-H bond has been replaced by an sp^3 carbon-halogen (C-X) bond, and (b) where there is at least one other hydrogen atom attached to that carbon atom (i.e., the carbon does not have three other alkyl groups in addition to the halogen atom, so the structure can be CH_3X, RCH_2X, or R_2CHX, but not R_3CX). In the three cases where there is at least one hydrogen atom still attached to the carbon, which are called unhindered sp^3 C-X bonds, the compound can participate in substitution reactions that are directly analogous with Brønsted acid-base reactions, in which the carbon atom plays the role of the hydrogen atom in a Brønsted acid (Figure 0418 on the next page).

For example, if the hydrogen atom of HBr is replaced by a CH_3 group, the carbon meets the two criteria listed above (it is an sp^3 carbon atom with at least one hydrogen atom attached to it). This CBr bond can undergo a substitution reaction with ammonia in which a new CN bond is formed and the CBr bond is broken. And by direct analogy, the mechanism of the reaction is also one in which the two bond-change events occur simultaneously. Both the energy diagram and the transition state structure are analogous. The biggest difference between the two reactions is that the transition state structure is more crowded, and the collision is harder to do with the carbon atom of CH_3Br than with the hydrogen atom of HBr because it is on the interior of the molecule. The ammonia needs to hit the carbon along a much narrower trajectory, and get past those hydrogen atoms of the CH_3 group on the way in. Consequently, the energy of the transition state is higher for the collision with CH_3Br than it is for HBr, and the reaction would be expected to be slower under comparable experimental conditions.

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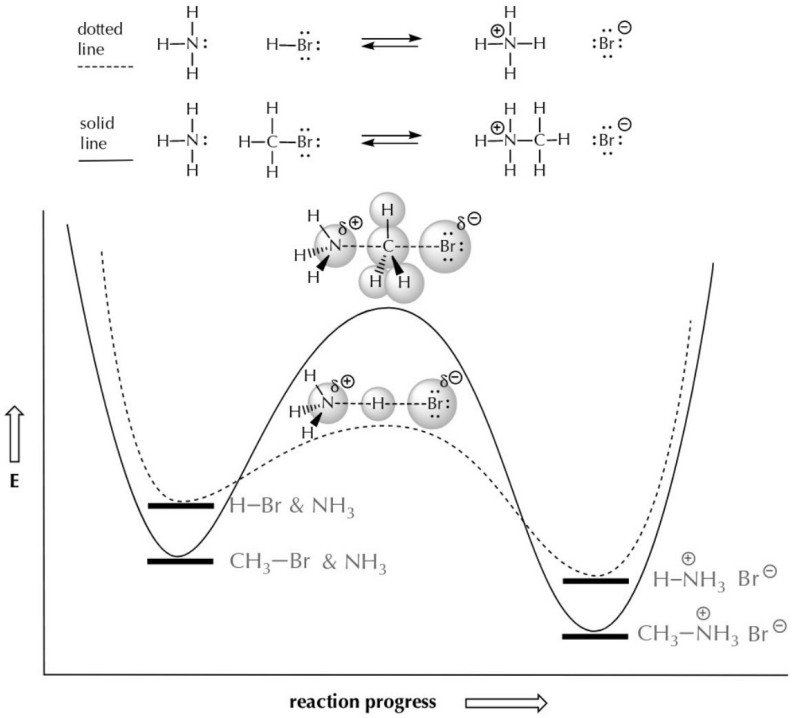
Figure 0418

Comparison between the substitution reactions of ammonia with HBr and CH_3Br.



As mentioned above, not all carbon-halogen bonds are observed to undergo this collisional substitution reaction pathway. Experimentally, compounds with hindered sp^3 C-X bonds (R_3CX) have never been observed to react by this collisional analogy with acid-base reactions. The three alkyl (R) groups create an environment in the molecule, in the vicinity of the CX bond, that is too crowded for a direct collision (the activation energy is too high). Neither sp^2 nor sp CX bonds are observed to undergo these collisional substitution reactions, either, which is also attributed to activation energies that are too high. A diverse sampling of substitution reactions of sp^3 C-X bonds, under their Brønsted acid-base counterparts, are shown in Figure 0419.

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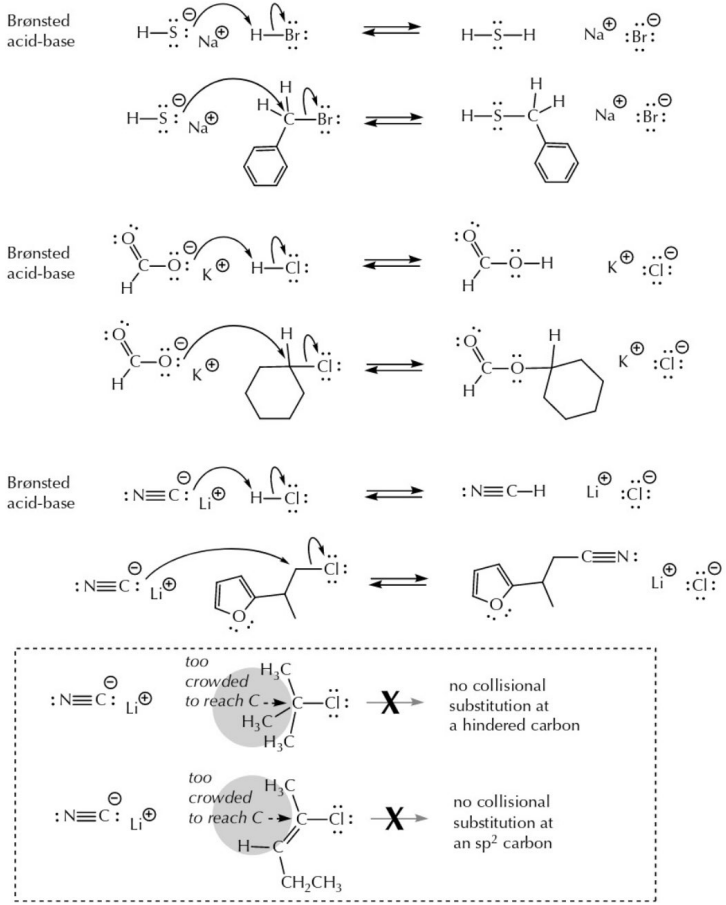
Figure 0419

Reaction analogies: substitution at hydrogen versus substitution at carbon.


Brønsted acid-base
Brønsted acid-base
Brønsted acid-base
too crowded to reach C
no collisional substitution at a hindered carbon
too crowded to reach C
no collisional substitution at an sp² carbon

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D. General Considerations for Competing and Multistep Reaction Mechanisms

So far, the energy diagrams in this presentation are all for simple reactions: one starting point, one ending point, and occurring in a single step. Many organic reactions are more complex than this, involving multiple pathways (where there is more than one outcome) and involving multiple steps in the reaction mechanism.

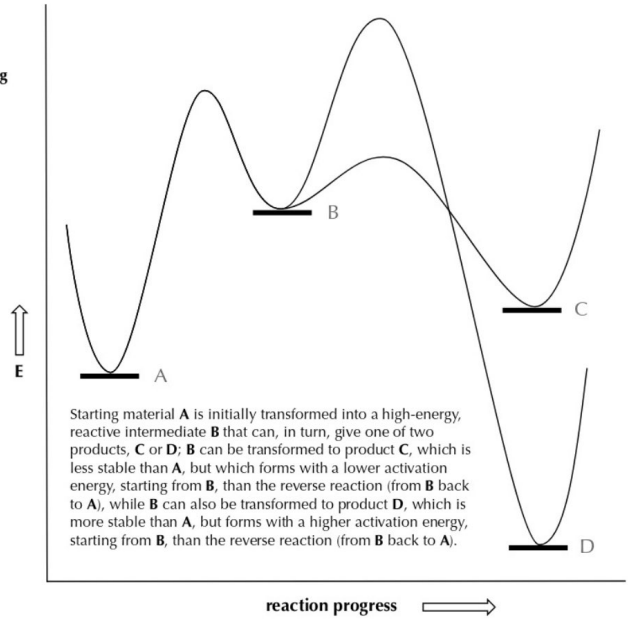
Energy diagrams can provide a convenient and efficient way to discuss the different outcomes that might be expected under different experimental and/or mechanistic conditions. The next short paragraph describes a set of relationships between four compounds, called **A**, **B**, **C**, and **D**.

> Sticking with an abstract example for the moment, imagine how to represent the following reaction: Starting material **A** is initially transformed into a high-energy, reactive intermediate **B** that can, in turn, give one of two products, **C** or **D**; **B** can be transformed to product **C**, which is less stable than **A**, but which forms with a lower activation energy, starting from **B**, than the reverse reaction (from **B** back to **A**), while **B** can also be transformed to product **D**, which is more stable than **A**, but forms with a higher activation energy, starting from **B**, than the reverse reaction (from **B** back to **A**).

That's quite hard to follow! As pointed out in the introductory essay in this chapter, sometimes a drawing or a diagram does a much better job than text does at representing an idea.

The energy diagram in Figure 0420 represents exactly the same ideas as this complicated text passage (the text is included, follow along), but it allows you to see the various relationships all at once rather than one at a time. The paragraph is included with the figure, and you should read it again in the context of the drawing, to experience how having the diagram and the text work together.

Figure 0420
Graphical versus text comparison for describing a multistep mechanism.


B
C
A
E
D
Starting material A is initially transformed into a high-energy, reactive intermediate B that can, in turn, give one of two products, C or D; B can be transformed to product C, which is less stable than A, but which forms with a lower activation energy, starting from B, than the reverse reaction (from B back to A), while B can also be transformed to product D, which is more stable than A, but forms with a higher activation energy, starting from B, than the reverse reaction (from B back to A).
reaction progress

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There is more information contained in Figure 0420. Reading the energy diagram in the usual left to right direction (the forward reaction), there is one starting material (**A**) and two products (**C** and **D**), all with ground state energies at relative energy minima (valleys). Any energy minimum between a starting material and a product (e.g., **B**) is called an intermediate. Getting from **A** to **C** is shown as a two-step mechanism that proceeds through the intermediate **B**; there are two transition states from **A** to **C**, one for each of the mechanistic steps (**A** to **B**, and **B** to **C**). Getting from **A** to **D** is comparable: two mechanistic steps (**A** to **B**, and **B** to **D**), each with its own transition state, and the one intermediate (**B**) from which both **C** and **D** are formed. There are three choices at intermediate **B**, based on the three available pathways with three different activation energies. If all steps are possible, then, starting from **B**, the rate of formation of **C** is always faster than the rate of return to **A**, which is always faster than the rate of formation of **D**. Molecules cannot know the relative depths of the valleys into which they are headed, only the expectation that the rate of passage over a barrier with a lower activation energy is faster than a higher one.

The need to narrate an illustration, or to illustrate a text narrative, is pervasive in how chemistry is understood. Because the words and pictures work together, you should begin to automatically expect to tell the story of any given drawing, or to produce a drawing that illustrates a point you want to make. Figure 0421 reproduces the same drawing of the energy diagram used in Figure 0420, and three different cases ("stories") are told about compounds **A**–**D**, depending on which of the steps are reversible and which are irreversible. These three narratives are tied to the drawing and need to be read with reference to those relationships.

Figure 0421

Topics in multistep reaction mechanisms: thermodynamic versus kinetic control, rate-determining steps.

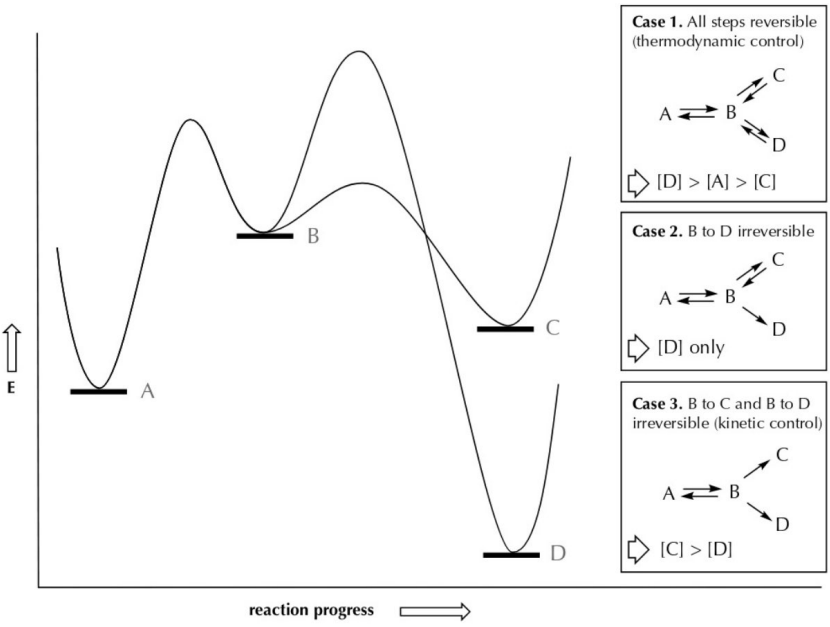

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Figure 0421 (Case 1): In a mechanism, any step might be reversible; that is, it is possible to go from **A** to **B** and from **B** to **A**. Or, the step might be irreversible, where it is possible to go from **A** to **B** but not back from **B** to **A**. If all of the steps are reversible, then the overall reaction outcome is based on the relative stability of all of the compounds. With reference to the illustration in Figure 0421, this means that, at equilibrium, product **D** will be the most abundant, then the starting material **A**, then the product **C**. In general, intermediates such as **B** are high in energy and also reactive, so they have no substantial lifetime and are not easily observed. Small energy differences are exponentially related to concentration differences (i.e., differences in ΔG°, which is related to log(K_{EQ}) are linear while differences in K_{EQ} themselves are exponential, so while K_{EQ}'s 10^2 and 10^6 are different by a factor of 10,000, the log difference is only a factor of 3, that is, 2 versus 6). In other words, a small difference in energy corresponds to a large difference in concentration.

When all of the steps are reversible, and the relative stabilities dictate the outcome, this is referred to as a reaction under thermodynamic control. The most stable product is not necessarily the one that forms fastest, however (the molecules are not psychic). One of the products might form faster, but if it forms reversibly, then an equilibrium can be established between two products of different stability, and this difference dictates the ultimate outcome, favoring the more stable product.

Looking at the rates at which the products form requires looking at the relative activation energies. In the transformation of **A** to **D**, the second step (**B** to **D**) has a transition state structure with the higher absolute energy than the first step (**A** to **B**). In a multistep mechanism, the step involving the transition state structure with the highest absolute energy is referred to as a rate-determining step (rds). That is, progress from **A** to **D** is limited by the rate at which **B** goes to **D**, because when you are at point **B**, the rate of going back to **A** is faster than going forward to **D**, so heading back to the starting material is more favorable than heading to the product. On the other hand, for the transformation of **A** to **C**, the first step has the transition state of highest absolute energy of that pair, and once you are over the **A** to **C** step, the rate to the product (**B** to **C**) is faster than the rate back to the starting material (**B** to **A**), and so the **A** to **B** step is the rds for the **A** to **C** transformation. It is easy to make the error that the rate-determining step is a comparison of relative activation energies; it is not. In a multistep sequence, the rate-determining step is the one that involves the transition state structure with the highest absolute energy.

Figure 0421 (Case 2): In Case 2, the **B** to **D** step is assigned as irreversible (**B** can be transformed to **D**, but **D** cannot return to **B**), while all of the other steps are still reversible. Under these nonequilibrium conditions, only **D** is expected. It will take a little time to happen, but every time the **B** to **D** step happens, the molecule is stuck there at **D**, unable to return to **B**. As the intermediate **B** forms, its choices are to return to **A** or proceed to **C** or **D**. The only thing that matters to **B** is the relative size of the three activation energies it faces. Its rate of transformation to **C** is faster than its return to **A**, and both of these are faster than the transformation to **D**. But forming **C** and returning to **A** are two-way streets, and **B** continues to be reformed from both **A** and **C** because those steps are reversible. But every time the **B** to **D** path is taken, there is no return, and all of the molecules eventually and completely (in theory) accumulate as **D**. If the **B** to **C** step had been the irreversible one, then all of the molecules would have accumulated as **C**.

Figure 0421 (Case 3): In Case 3, both the **B** to **D** and **B** to **C** steps are assigned to be irreversible steps. Now there will be a distribution of products **C** and **D**, favoring **C**. The decision point on the outcome is pushed back to position **B**, as passage to both **C** and **D** are both one-way streets with no return. Recall that, at point **B**, the molecules cannot possibly know which of the two available pathways gives a more stable product; we simply have the case of more molecules having enough energy to pass over the lower activation energy (a faster rate) than passing over the higher activation energy (a slower rate). The magnitude of the **C**:**D** ratio will not depend on the difference in energy between **C** and **D**, but rather in the difference in activation energies for the **B** to **C** step versus the **B** to **D** step. In this case, where the relative reaction rates dictate the outcome, the reaction is referred to as being under kinetic control.

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PRACTICE QUESTIONS

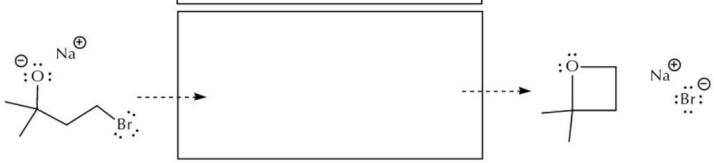
4.04 Each of the following transformations is proposed to take place in one mechanistic step. Provide a drawing of the anticipated transition state structure. Use dotted lines for partial bonds and indicate the appropriate non-bonding electron pairs and partial charges, as needed.

(a)

(b)

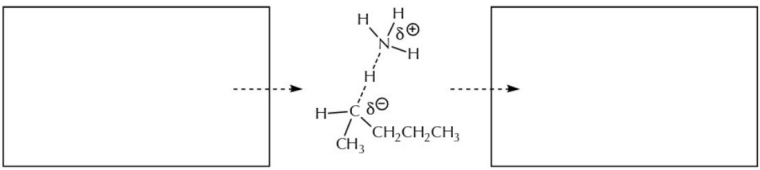
(c)

(d)

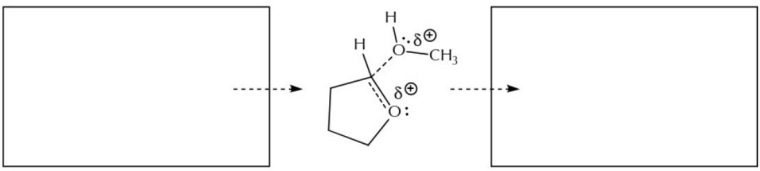


4.05 A transition state structure is shown in each of these examples. Provide starting point and ending point structures that are consistent with this transition state. Because a transition state structure does not define the direction of a reaction, there are multiple possible answers (all structures should have closed shell atoms).

(a)



(b)



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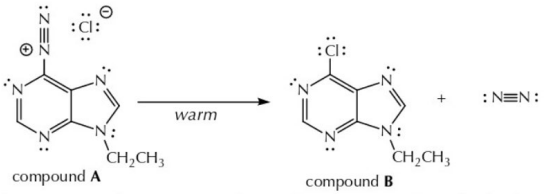
4.06 The following chemical reaction is modeled on a literature report (*J Org Chem*, **2002**, *67*, 6788). The experimental evidence was consistent with a substitution mechanism that took place at an sp^2 carbon, the mechanistic details for which are included below. Follow the guidance to construct the proposed mechanism.



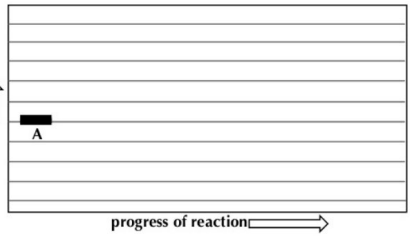
This reaction has a 2-step mechanism. First, in the rate determining step, the molecule of nitrogen decomplexes from the carbon to which it is attached in compound **A** to form a carbocation intermediate (**I**). Then, the carbocation combines quickly with chloride ion to give the observed product (compound **B**), which is not only more stable than compound **A**, but forms irreversibly because of the loss of nitrogen gas.

(a) Provide the curved arrow mechanism for the formation of the carbocation intermediate **I**, the structure for carbocation **I**, as well as the curved arrow mechanism for the formation of compound **B** from intermediate **I**.

(b) Provide a drawing of the transition state structure anticipated for the transformation of compound **A** to the carbocation intermediate **I**, using dotted lines for partial bonds and indicate partial charges and nonbonding electrons where appropriate.

(c) Complete this energy diagram for this chemical reaction. Place (i) the energies of intermediate **I** (plus chloride), (ii) the product compound **B**, and (iii) the curves that represent the energy changes for each step through the transition states. Then (iv) circle the position of the transition state you drew in part (b).

Note: Horizontal grid lines have been added so you can better gauge how you draw your relative energy levels (i.e., higher versus lower, no units are given).



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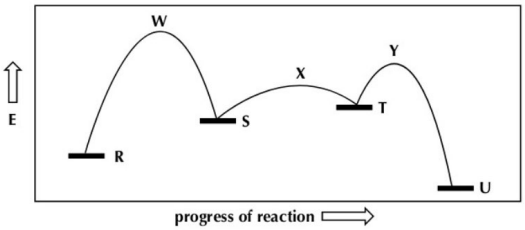
4.07 The energy diagram for the conversion of Compound **R** to Compound **U** is shown below.



Reply to the following with either a number, or by placing the letter or letters corresponding to the points on this diagram.

(a) How many mechanistic steps are implied for the conversion of **R** to **U**?

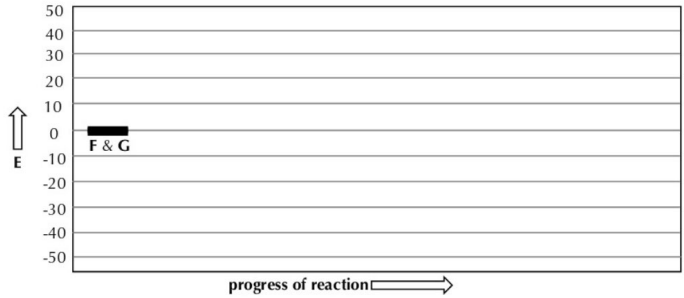
(b) How many transition states are shown for the conversion of **R** to **U**?

(c) What is the rate-determining step for the conversion of **R** to **U**?

(d) If all steps are reversible, which compound will be present at the highest equilibrium concentration?

(e) Which step, among all forward and reverse steps, has the lowest energy of activation?

4.08 The energy of activation for the reaction between compounds **F** and **G** is 40 kcal/mol, and the product, compound **H**, is 35 kcal/mol more stable than the **F**/**G** pair. The energy of activation for the transformation of compound **H** to compound **J** is 15 kcal/mol, and compound **J** is 10 kcal/mol more stable than compound **H**. Draw an energy diagram for the transformation of **F** and **G** to compound **H**, then to compound **J**, on the following graph. The horizontal line on the left is the starting energy level for the **F**/**G** pair. Include: (a) the energy levels for compounds **H** and **J**; (b) the curves that represent the energy changes during the course of the reaction; and (c) an arrow that points to the spot of the diagram corresponding to the transition state for the formation of compound **H** and label it "TSH" for "transition state leading to compound **H**."



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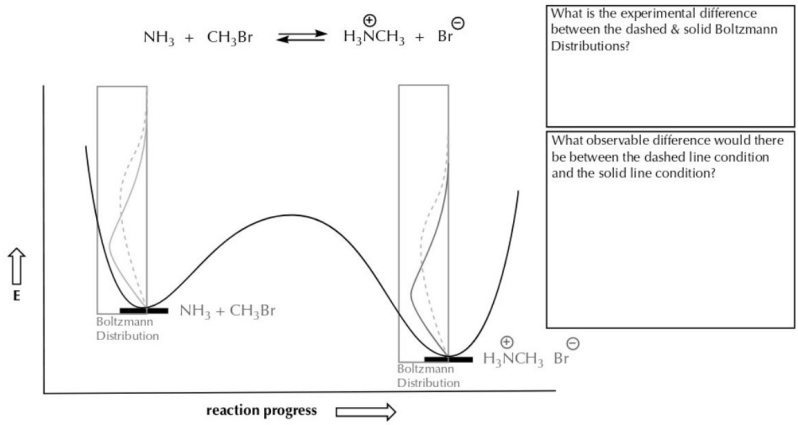
4.09 The following energy diagram is for the substitution reaction between ammonia (NH_3) and bromomethane (CH_3Br).

(a) What is the difference in experimental conditions for the two different Boltzmann Distributions shown in both of the vertical boxes (dashed lines versus solid lines)? Explain, using the difference in the distributions, what experimental difference would be observed, and why, in changing from the solid to the dashed line conditions.

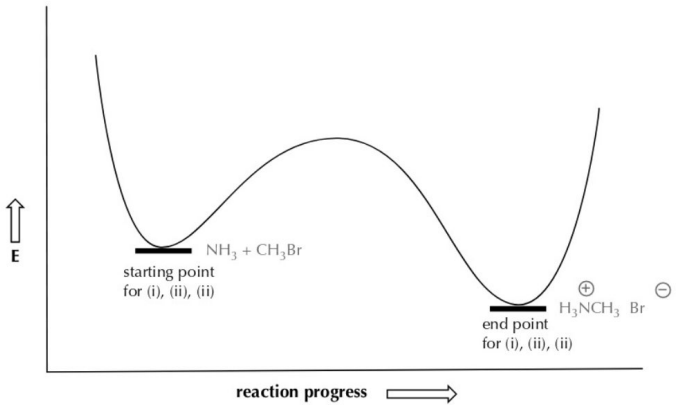

NH3 + CH3Br ⇌ H3NCH3 + Br
What is the experimental difference between the dashed & solid Boltzmann Distributions?
What observable difference would there be between the dashed line condition and the solid line condition?
E
NH3 + CH3Br
Boltzmann Distribution
H3NCH3 Br
Boltzmann Distribution
reaction progress

(b) Assuming that starting and end points for the energy diagrams of the following three reactions are superimposed on this same energy diagram (i.e., the 3 ΔG° values are the same), sketch in the three energy curves for the following three conditions, using the reaction above as the point of reference.

(i) $NH_3 + CH_3Br \rightleftharpoons H_3\overset{\oplus}{N}CH_3 + \overset{\ominus}{Br}$ with an effective catalyst (increases the rate)

(ii) $NH_3 + CH_3CH_2Br \rightleftharpoons H_3\overset{\oplus}{N}CH_2CH_3 + \overset{\ominus}{Br}$

(ii) $NH_3 + (CH_3)_2CHBr \rightleftharpoons H_3\overset{\oplus}{N}CH(CH_3)_2 + \overset{\ominus}{Br}$



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4.3 Electrophilic Addition Reactions of Strong Brønsted Acids

A. Observed Outcomes, Structural Classifications, and Regioselectivity

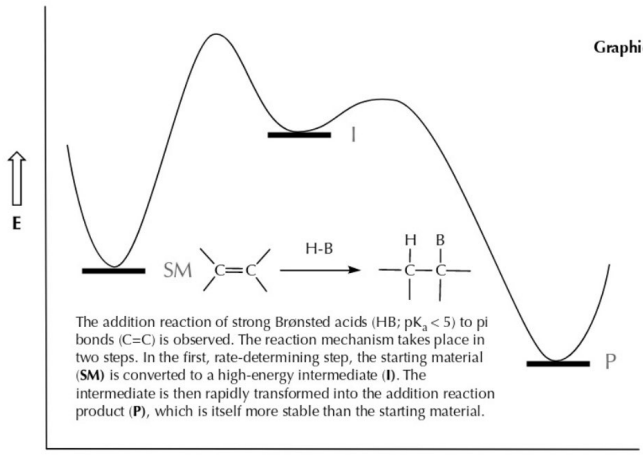
The second half of this chapter draws strongly from its first two sections. For example, the following statement does not contain any new words or ideas, but rather combines the previous concepts to communicate details about an organic reaction. If you find yourself wanting a drawing to go along with this, you are starting to pick up a critical lesson about organic chemistry.

> *The addition reaction of strong Brønsted acids (HB; $pK_a < 5$) to pi bonds (C=C) is observed. The reaction mechanism takes place in two steps. In the first, rate-determining step, the starting material (**SM**) is converted to a high-energy intermediate (**I**). The intermediate is then rapidly transformed into the addition reaction product (**P**), which is itself more stable than the starting material.*

A second lesson about organic chemistry is also exemplified in this statement, namely, how foundational information is used to build and communicate larger ideas. The statement shows how critical it is to understand the prior ideas, because this new statement builds upon them and it is nearly impossible to appreciate what this statement is saying without understanding those prior ideas. For example, this statement assumes that you understand all of these terms and that you do not need to be taught what they are: Brønsted acid, addition reaction, pK_a, pi bonds, mechanism, rate-determining step, intermediate. Decoding the statement starts with the big idea: The topic is addition reactions (Section 4.01C). Then, the story about the reaction mechanism is provided. Although it does not say so explicitly, the statement refers to the features that are associated with an energy diagram, which is yet another association that needs to be made by the reader.

Figure 0422 illustrates how this statement can be re-represented, based upon the information from earlier in the chapter—*and nothing new*. Key features for the energy diagram: (1) two steps: **SM** to **I**, **I** to **P**; (2) **P** is lower in energy (most stable) than **SM**; (3) the energy level of **I** is higher than both **SM** and **P**; (4) the first step is rate-determining, so the absolute energy level of the transition state structure getting from **SM**

Figure 0422
Graphical interpretation of a reaction statement.


E
I
SM
H-B
H
B
P
reaction progress
The addition reaction of strong Brønsted acids (HB; pK$_a$ < 5) to pi bonds (C=C) is observed. The reaction mechanism takes place in two steps. In the first, rate-determining step, the starting material (SM) is converted to a high-energy intermediate (I). The intermediate is then rapidly transformed into the addition reaction product (P), which is itself more stable than the starting material.

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to **I** is higher than that for **I** to **P**. And although it is not critical to drawing the energy diagram, the overall reaction is specified as an addition reaction of HB to a pi bond, and this can be represented generically. As in an earlier figure, the text of the statement is included with the drawing so that you can re-read it in the context of the illustration.

Before getting to the details of this or any other reactions, it is useful to understand a bit more about the terms that organic chemists use when writing and speaking about molecular structures and their drawings of molecular structures. The structural classification introduced below is called the "degree of substitution."

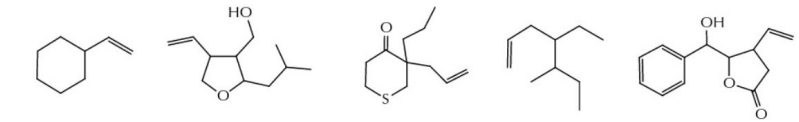
To help express ideas about chemical structural relationships using text, organic chemists developed a language of structural classification. The "degree of substitution" terminology is based upon the concept of "substitution" as a replacement relationship that is used in substitution reactions (Section 4.1B), while not implying that an actual reaction has taken place.

For example, when two tetravalent carbon atoms are double bonded, both carbons also have two valence sites for making two other bonds. The C=C, then, has four available bonding sites to complete its structure, and those sites can be occupied by four hydrogen atom groups, four hydrocarbon groups, or a combination of those groups. Using the all-hydrogen case as a point of reference, a double bond in which a hydrocarbon groups replaces one of the hydrogen atoms is called a monosubstituted double bond (Figure 0423). The degree of substitution of these double bonds is classified as monosubstituted regardless of the specific identity of the hydrocarbon group, in part because this class of molecules shows comparable chemical reactivity and properties.

Within an organic structure, saturated hydrocarbon groups are called "alkyl" groups and symbolized by the capital letter "R" (Section 2.1A). Both of these naming conventions derive from the early days of organic chemistry, when the hydrocarbon portion of alcohols was called the "alkoholradicale." In these examples of monosubstituted double bonds, we would say that an alkyl group has replaced one of the hydrogen atoms of the unsubstituted double bond (again, not as an actual reaction, but as a way to describe the structural relationship). The alkyl group is then referred to as a "substituent" or as a "substituent group" on the double bond.

Figure 0423
Monosubstituted double bonds.

Monosubstituted double bonds (generic representation)



Double bonds have five different degrees of substitution. They can be classified as unsubstituted (all four bonding sites occupied by hydrogen atoms), monosubstituted (one of the hydrogen atoms replaced by an alkyl substituent group, as above), disubstituted (two of the hydrogen atoms replaced), trisubstituted (three of the hydrogen atoms replaced), and tetrasubstituted (all four hydrogen atoms replaced).

The two carbons of a double bond are commonly referred to as the two "ends" of the double bond. If the number of substituent groups is the same at each end (that is, at each of the two carbons of the double bond), then the double bond is said to be equally, or symmetrically, substituted. If the number of substituent groups is different at two carbon atoms, then the double bond is unequally, or unsymmetrically, substituted, and the carbon with more substituent groups will be referred to as "the more substituted end of the double bond" or that it possesses a "higher degree of substitution." (Figure 0424)

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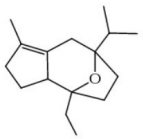
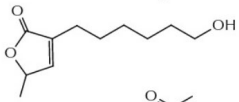
The degree of substitution terminology is generally used for replacements of hydrogen atoms by hydrocarbon groups. Groups based on the replacement by other atoms (N, O, S, etc.) are called heteroatom groups, and the point of reference is not always the double bond when these molecules are classified.

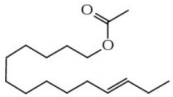
Figure 0424
Double bonds can vary in their degree of substitution.



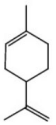
a tetrasubstituted double bond (prepared during the synthesis of a potential antitumor agent): both ends are equally substituted



a trisubstituted double bond (prepared during the synthesis of a compound used by soft corals to defend themselves): the top end, as drawn, is more highly substituted than the bottom end

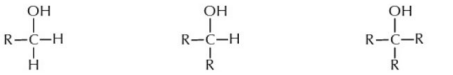


a disubstituted double bond (one of the components of the sex attractant pheromone of the Tea Tortrix moth): both ends are equally (although not identically) substituted

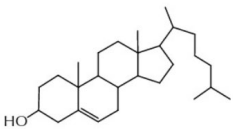


limonene (a natural oil found in lemon and orange peels) has two unsymmetrically substituted double bonds: a trisubstituted double bond (top of drawing - the left end, as drawn, is less substituted than the right end) and a disubstituted double bond (bottom of drawing - the left end, as drawn, is more substituted than the right end)

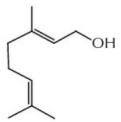
Figure 0425
Alcohols can vary in their degree of substitution.



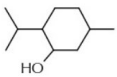
primary (1°) alcohol secondary (2°) alcohol tertiary (3°) alcohol



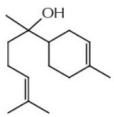
cholesterol contains a secondary (2°) alcohol and a trisubstituted double bond



geraniol, from the oil of the Turkish geranium flower, contains a primary (1°) alcohol and two trisubstituted double bonds



menthol, from peppermint oil, contains a secondary (2°) alcohol



bisabolol, from chamomile and lavender oils, contains a tertiary (3°) alcohol and two trisubstituted double bonds

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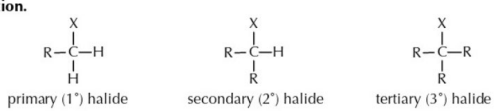
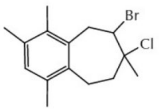
Some functional groups other than double bonds also use the degree of substitution terminology. The simplest member of the functional group family is used as the point of reference. For example, the simplest molecule called an alcohol has a hydroxyl group (OH) attached to one carbon atom, and that carbon atom, in turn, is only attached to three hydrogen atoms ($HOCH_3$). This molecule, methanol, is the point of reference for classifying alcohols, and this molecule would be called a completely unsubstituted alcohol. As this carbon's hydrogen atoms are replaced by alkyl groups, the classification of the resulting alcohol moves to higher and higher degrees of substitution. By historical convention, the monosubstituted alcohols are called "primary alkyl alcohols" or just "primary alcohols" ($HOCH_2R$). The term "primary" can also be represented by the "1°" notation (meaning "first degree of substitution"). Disubstituted alcohols are called secondary alcohols (2°; $HOCHR_2$), and trisubstituted alcohols are called tertiary alcohols (3°; $HOCR_3$). Examples of alcohol classification are provided in Figure 0425, found on the previous page.

Molecules with carbon-halogen bond functional groups (alkyl halides) are classified the same way as alcohols are (Figure 0426).

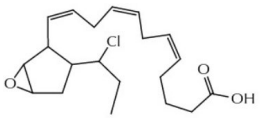
Figure 0426

Alkyl halides can vary in their degree of substitution.

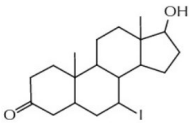




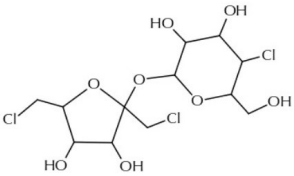
Perforene, a natural compound isolated from a marine fungus, contains a secondary (2°) bromide and a tertiary (3°) chloride (the double bonds here are part of a benzene ring structure, which has a different classification system)



egregiachloride C, isolated from a brown algae, contains a secondary (2°) chloride and three disubstituted double bonds (the hydroxyl group is not an alcohol functional group because it is directly attached to the carbon atom of a C=O group, a combination called a carboxylic acid group)



a synthetic anabolic steroid with androgenic biological activity, contains a secondary (2°) iodide and a secondary (2°) alcohol



sucralose (brand name Splenda), prepared from sucrose, contains two primary (1°) chlorides, one secondary (2°) chloride, one primary (1°) alcohol, and four secondary (2°) alcohols

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The degree of substitution terminology is also used to classify hydrogen atoms when they are part of a saturated hydrocarbon structure (no nearby heteroatoms or multiple bonds), as well as for carbon and nitrogen atoms, based on the number of attached alkyl groups. As with double bonds, saturated carbon and nitrogen can be tetrasubstituted with alkyl groups, and these are called quaternary (4°) atoms (Figure 0427).

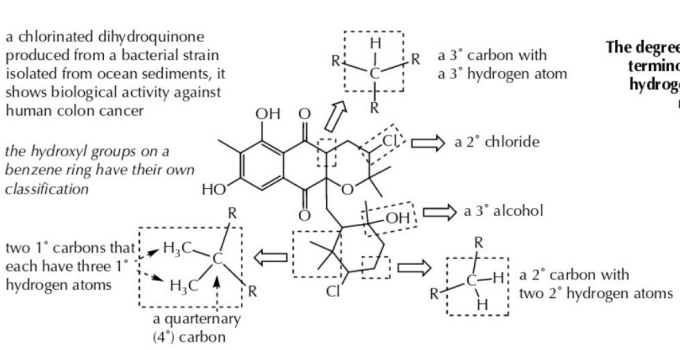
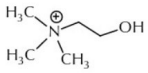
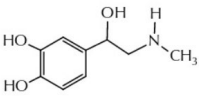

a chlorinated dihydroquinone produced from a bacterial strain isolated from ocean sediments, it shows biological activity against human colon cancer
the hydroxyl groups on a benzene ring have their own classification
a 3° carbon with a 3° hydrogen atom
a 2° chloride
a 3° alcohol
two 1° carbons that each have three 1° hydrogen atoms
a quaternary (4°) carbon
a 2° carbon with two 2° hydrogen atoms

Figure 0427
The degree of substitution terminology applied to hydrogen, carbon, and nitrogen atoms.



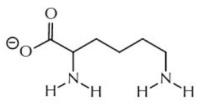
choline, an essential nutrient found in many foods, including eggs, chicken, almonds, cauliflower, and soy; the precursor to the vital neurotransmitter, acetylcholine

choline has a quaternary (4°) nitrogen and a primary (1°) alcohol



epinephrine, also known as adrenaline, is a hormone that stimulates the "fight or flight" response

epinephrine has a secondary (2°) nitrogen and a secondary (2°) alcohol



lysine is an amino acid that is an essential nutrient, that is, it cannot be synthesized by the body and must therefore be eaten; it can be found in most dairy products, fruits, fish and meats

lysine has two primary (1°) nitrogens

In summary, the degree of substitution classification system allows you to speak and write about some general features of organic structures without always needing to point to the drawing! The system is commonly used when describing the structure of double bonds, heteroatom functional groups such as alkyl alcohols and alkyl halides, and for carbon and nitrogen atoms embedded within a larger structure.

We will return now to decoding the statement written at the start of this section (reproduced here):

> *The addition reaction of strong Brønsted acids (HB; $pK_a < 5$) to pi bonds (C=C) is observed. The reaction mechanism takes place in two steps. In the first, rate-determining step, the starting material (**SM**) is converted to a high-energy intermediate (**I**). The intermediate is then rapidly transformed into the addition reaction product (**P**), which is itself more stable than the starting material.*

The first sentence in this statement sets up an observation: *The addition reaction of strong Brønsted acids (HB; $pK_a < 5$) to pi bonds (C=C) is observed.*

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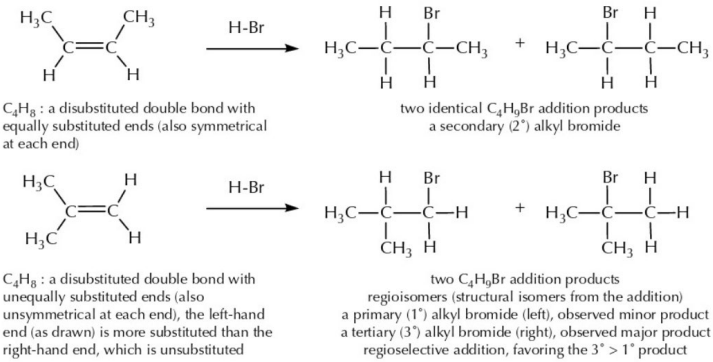
As you start to study new reactions, it is important to remember that these general statements are derived from thousands and thousands of different experiments. They are not deduced from theory. Once it appears that there is a general sort of observed reactivity, chemists will then turn their attention to figuring out what is going on. And so, the statement above (addition reactions of strong Brønsted acids and pi bonds are observed) is communicating information that provides the context, or framework, for the detailed explanation. The explanation, in turn, builds towards the observation, and pieces of the explanation that are inconsistent with the observation are rejected. In other words, it does not matter how beautiful or compelling a model of sunrise-sunset might be if it predicts that the sun rises in the west and sets in the east. The observation (experimental reality) is used to accept or reject explanations.

Addition reactions can often result in two structural isomers. Except for molecular hydrogen (H-H), Brønsted acids (H-B) are inherently unsymmetrical. Because a double bond has two ends, the addition of the "H" and "B" components to a double bond may or may not result in two different products, depending on whether the double bond is symmetrical or unsymmetrical. Two addition reactions between a couple of C_4H_8 isomers and HBr to give an array C_4H_9Br products are shown in Figure 0428.

Figure 0428

Addition reaction of HBr with a symmetrical and unsymmetrical double bond.



C_4H_8 : a disubstituted double bond with equally substituted ends (also symmetrical at each end)

two identical C_4H_9Br addition products a secondary (2°) alkyl bromide

C_4H_8 : a disubstituted double bond with unequally substituted ends (also unsymmetrical at each end), the left-hand end (as drawn) is more substituted than the right-hand end, which is unsubstituted

two C_4H_9Br addition products regioisomers (structural isomers from the addition) a primary (1°) alkyl bromide (left), observed minor product a tertiary (3°) alkyl bromide (right), observed major product regioselective addition, favoring the 3° > 1° product

In the first case, the disubstituted double bond is equally substituted at each end, and the molecule, itself, is completely symmetrical (that is, the same $-CH_3$ alkyl substituent appears at both ends of the double bond). Although the addition reaction of HBr can proceed in two ways ("H" on the left, "Br" on the right, and vice versa), the two outcomes are identical, producing the same secondary (2°) alkyl bromide.

In the second case, the double bond is still disubstituted, but it is unequally substituted. There are two $-CH_3$ alkyl substituents on one end (the more substituted end) and only hydrogen groups at the other end (the unsubstituted end). The double bond is inherently unsymmetrical, and the two different addition pathways for HBr result in different alkyl bromides, a tertiary (3°) one and a primary (1°) one.

When two or more structural isomers form in a reaction, differing because of the position (structural region) of the resulting functional group, they are called regioisomers. Returning to the first case in Figure 0428 with this new vocabulary, the two addition outcomes are identical and so they are not regioisomers. In

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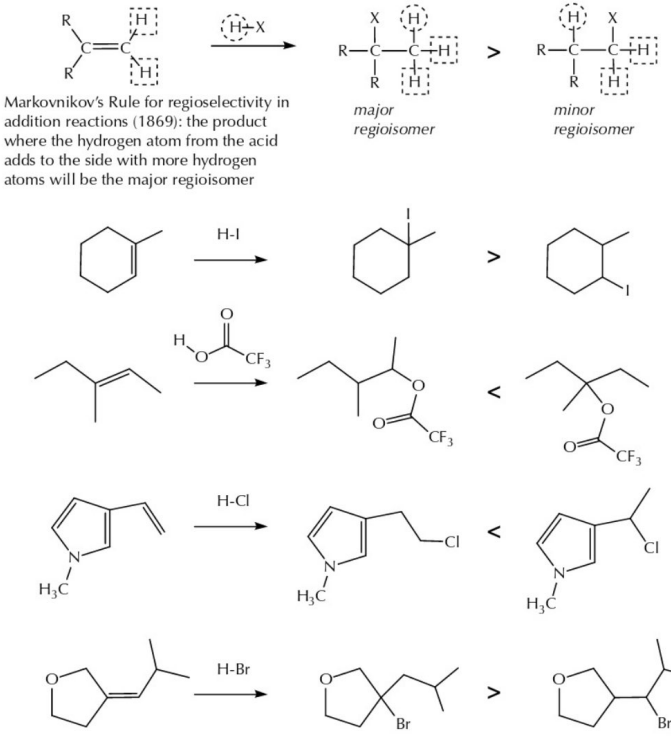
the second case, the primary and tertiary alkyl bromide products are called regioisomers. The degree to which one regioisomer is formed in preference to another is called the regioselectivity of a reaction. If there are regioisomers and they form in equal amounts (50:50 in the case of two possible regioisomers), then the reaction is said to show no regioselectivity. If there are regioisomers and only one is produced, then the reaction is said to show complete regioselectivity.

The addition reactions of Brønsted acids to unsymmetrical double bonds generally show regioselectivity. In the second case in Figure 0428, the tertiary alkyl bromide is experimentally observed to be the major product, while the primary alkyl bromide is a minor product. The experimental ratio is high, so the reaction is said to show a high regioselectivity in favor of the tertiary product. Again, no explanation for the regioselectivity is being given (yet), just the report of the experimental observation. In fact, historically, this observation of regioselectivity in addition reactions predates any explanation by decades.

The origins of regioselectivity. A few models have been used for predicting the regioselectivity of these reactions over the years. In the first of these (1869), a Russian chemist named Vladimir Markovnikov

Figure 0429

Regioselectivity of addition reactions of strong Brønsted acids ($pK_a < 5$) according to the original Markovnikov Rule.



Markovnikov's Rule for regioselectivity in addition reactions (1869): the product where the hydrogen atom from the acid adds to the side with more hydrogen atoms will be the major regioisomer

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observed a general trend: A Brønsted acid (HB) would favor adding to an unsymmetical double bond so that the "H" atom partner from the H-B reagent was bonded to the end of the double bond that originally had more hydrogen atoms. Note that this description is true for the second case in Figure 0428, where, in the major regioisomer (the tertiary halide) the hydrogen atom from HBr is bonded to the end of the double bond that originally had two other hydrogen atoms rather than none.

> *"When a hydrocarbon of unsymmetrical structure combines with a halogen hydracid, the halogen adds itself to the less hydrogenated carbon atom, i.e., to the carbon atom that is more under the influence of other carbon atoms." —Vladimir Markovnikov, 1869*

This experimental observation for the regioselectivity does not explain the regioselectivity, but it applied to many reported cases and was a useful enough generalization that it was called Markovnikov's Rule. Over the years, chemists have come to understand the detailed reasons for the regioselectivity in these and other reactions, and the Markovnikov Rule has evolved, accordingly. Still today, however, it is common to hear chemists refer to an addition reaction as having a Markovnikov regioselectivity. Figure 0429 on the previous page contains examples of reactions that follow Marnovnikov's original generalization for addition reactions showing high regioselectivity.

B. Proposed Stepwise Mechanism: The Carbocation Intermediate

During the mid-20th century, physical organic chemists developed experimental methods that are still in use today, such as reaction rate studies, to work out the details of reaction mechanisms. The summary statement that led off this section is a summary statement from the results of these experiments.

> *The addition reaction of strong Brønsted acids (HB; $pK_a < 5$) to pi bonds (C=C) is observed. The reaction mechanism takes place in two steps. In the first, rate-determining step, the starting material (**SM**) is converted to a high-energy intermediate (**I**). The intermediate is then rapidly transformed into the addition reaction product (**P**), which is itself more stable than the starting material.*

What is needed here is the illustration of the molecular description of the process: What does this first step look like? What is the intermediate? What is the second step?

We are not going to review the history, here, but instead we will jump to the results from hundreds of experiments done over many years. These results fill in detail to the statement, above, and these details cannot be deduced from the general observation because they were discovered experimentally. Once you learn what this generalized mechanism means, you can apply it to a countless number of new reactions that fit into the same category: The addition reaction of strong Brønsted acids (HB; $pK_a < 5$) to pi bonds (C=C).

The summary from years of experimentation is given by two concise statements:

In the first, rate-determining step, a pi bond is protonated by the strong Brønsted acid (HB) in highest concentration in solution to give the new C-H bond at one end of the double bond and a positively charged, open shell carbon (a carbocation) at the other end.

The high-energy carbocation intermediate is then rapidly captured by the conjugate base of the original Brønsted acid to form the new C-B bond, which completes the addition reaction.

With this information, you have complementary tools for understanding an organic chemical reaction. Markovnikov's Rule can be used to predict the regioselectivity of the overall outcome, and this two-step mechanism can be applied to create a detailed explanation.

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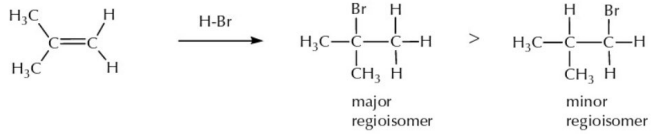
Returning to the second reaction in Figure 0428: When you know that an addition reaction takes place and you know it follows the Markovnikov Rule, you can draw the two possible regioisomers and, following the rule, tell which of them will be the major product (Figure 0430). The information that you can determine from the reaction classification and Markovnikov's Rule is substantial: You can predict the structure of the major product from a reaction. This prediction matched the observed outcome, and as a matter of principle, the mechanism of a reaction tells the detailed, stepwise, molecular story about an observed outcome.

Figure 0430

A regioselective addition reaction with HBr.



Because this reaction involves a strong Brønsted acid (as defined for these addition reactions, $pK_a < 5$), the two-step mechanism summarized above is expected to apply.

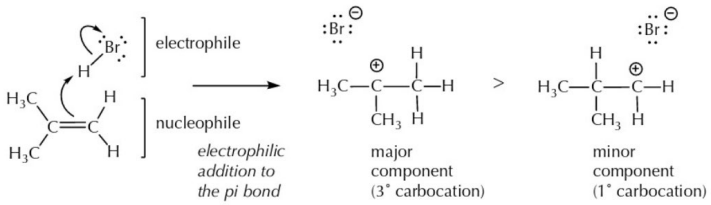
In the first step: *The pi bond is protonated by the strong Brønsted acid (HB) in highest concentration in solution to give the new C-H bond at one end of the double bond and a positively charged, open shell carbon (a carbocation) at the other end.*

The new information here, with respect to prior examples of acid-base chemistry, is that a pi bond can be protonated with a strong acid. Until now, you have only seen atoms with nonbonding electron pairs behave as electron donors towards Lewis and Brønsted acids. What the experiments revealed was evidence consistent with the idea that the electron pair of a pi bond could also be used to make a new sigma bond with proton donors. This reaction is shown in Figure 0431. The electron pair from a pi bond is drawn to HBr, the proton donor and strong acid in highest concentration, forming a new CH bond at one end of the double bond. Simultaneously, the electrons vacate the carbon atom at the other end of the double bond, leaving an open shell, positively charged atom called a carbocation.

Figure 0431

Mechanism of a regioselective addition reaction with HBr: step one.

In the first step: *The pi bond is protonated by the Brønsted acid in highest concentration in solution to give the new C-H bond at one end of the double bond and a positively charged, open shell carbon (carbocation) at the other end.*



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Because the double bond is unsymmetrical, the protonation of the double bond gives different carbocation intermediates depending on which end gets the proton. Because of the 1869 Markovnikov Rule, we can say that the protonation at the end of the double bond with more hydrogen atoms is preferred, although the underlying explanation for why is still an open question that will be taken up in the next section. The classification terminology can be used on the carbocation intermediates to make referencing them convenient. The carbocation with three alkyl groups (R_3C^+) is a tertiary (3°) carbocation, while the one with one alkyl group and two hydrogen atoms (RCH_2^+) is a primary (1°) carbocation. Because we know, from the observed regioselectivity and the Markovnikov Rule, that the major regioisomer is the one where the protonation takes place on the less substituted end of the double bond, the 3° carbocation is expected to be the major component and the 1° carbocation is expected to be the minor component.

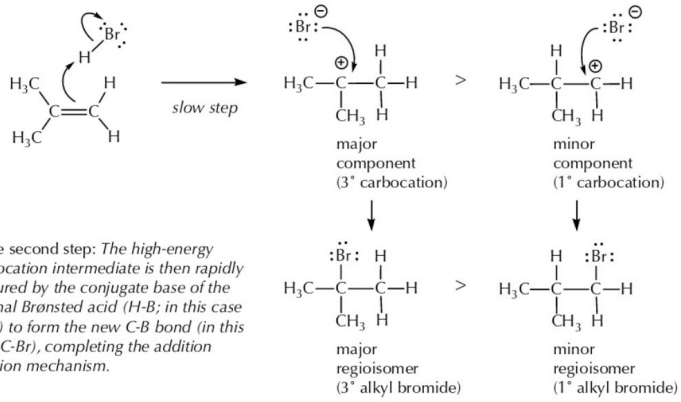
As you can see in this example, these organic chemical reaction mechanisms involve reactive partners that are more general than just Brønsted or Lewis acids and bases. What these reactions do have in common is the combination of a partner with an electron pair to donate towards a new bond (even at the expense of an old one) and a partner that accepts an electron pair (even at the expense of an old one). Today, the two most generic terms for these electron-donating and receiving partners are nucleophile and electrophile, respectively.

A nucleophile (translation: nucleus-loving) provides the electron pair to form a new bond (i.e., an atom with electrons to share is looking for a nucleus to share with), while the electron-receiving partner is the electrophile (translation: electron-loving). In the protonation reaction of a pi bond (Figure 0431), the pi bond is the electron donor in the first step, and so the molecule with the double bond is the nucleophile. The Brønsted acid is the electron-receiving partner, and so the electrophile. Depending on the role that is played by the pi bond, addition reactions are subclassified as either nucleophilic addition or electrophilic addition. When the pi bond reacts with an electrophile and uses its electrons to form a new bond in the first step, as in these examples, then it is classified as an electrophilic addition reaction.

Figure 0432

Mechanism of a regioselective addition reaction with HBr: step two.

In the first step: *The pi bond is protonated by the Brønsted acid in highest concentration in solution to give the new C-H bond at one end of the double bond and a positively charged, open shell carbon (carbocation) at the other end.*


slow step
major component (3° carbocation)
minor component (1° carbocation)
major regioisomer (3° alkyl bromide)
minor regioisomer (1° alkyl bromide)

In the second step: *The high-energy carbocation intermediate is then rapidly captured by the conjugate base of the original Brønsted acid (H-B; in this case H-Br) to form the new C-B bond (in this case C-Br), completing the addition reaction mechanism.*

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Now we can complete this two-step reaction mechanism.

According to the second step, *the high-energy carbocation intermediate is then rapidly captured by the conjugate base of the original Brønsted acid to form the new C-B bond, which completes the addition reaction.*

This step is a familiar Lewis acid-base reaction. We know from the original addition concept that a carbon-bromine bond is formed in the reaction. The carbocation intermediate is an open shell atom (a Lewis acid), and a bromide ion (a Lewis base) was released in the first step. Forming the required carbon-bromine bond follows from the chemistry of Lewis acids and bases (Section 3.1), as the carbocation is captured by the bromide ion. In this step, the bromide ion is the nucleophile and the carbocation is the electrophile (Figure 0432).

In the previous example, no details about the experimental conditions were provided. Actual laboratory experiments are more complex procedures than mixing two pure substances together. One piece of experimental information that is sometimes provided is the solvent. There are times when the solvent is inert (e.g., CCl_4, CH_2Cl_2, ether), and simply serves to help dissolve and mix the reagents. Other times, the solvent plays a role in the chemistry.

In these electrophilic addition reactions, the carbon-carbon pi bonds might not be the only thing getting protonated. If a solvent is included, and if that solvent is a good Brønsted base for the Brønsted acid (e.g., water, methanol, ethanol), then the fast and favorable Brønsted acid-base reaction will happen much faster than the protonation reaction of the pi bond, which is slower because it forms a high energy, open shell carbocation intermediate.

The presence of a solvent acting as a Brønsted base does not change the two steps of the addition reaction mechanism, and it is the reason why the phrase "the acid in highest concentration" is used in the description of the first step. In Figure 0433, the same reaction as in Figure 0432 is carried out, except that the Brønsted basic solvent, ethanol (CH_3CH_2OH) is present.

Although it is a convention that is not adhered to as a strict rule by chemists, in this text we will usually show the active reagents, whose atoms are combining with a starting material, above a reaction arrow, and show reaction conditions (temperatures, solvents, concentrations) below the reaction arrow. Therefore, when the conditions are drawn as depicted in Figure 0433, the writer is signaling to the reader that the elements of HBr are being added. As mentioned above, sometimes the solvent is inert and sometimes not even depicted, and the actual Brønsted acid that protonates the pi bond is assumed to be the reagent itself. But sometimes, the solvent plays a more active role in the mechanism, and the presence of the Brønsted basic solvent, ethanol (CH_3CH_2OH), is such an example.

Long before HBr can protonate the double bond to give an unstable carbocation, any other fast and favorable acid-base reactions will have happened. In Figure 0433, the reaction between HBr (~pK_a -8) and ethanol (conjugate acid ~pK_a -2) is quite favorable, and so there is no actual HBr in solution. Instead, the acid present in highest concentration is the conjugate acid of ethanol ($CH_3CH_2OH_2^+$ Br^-), and this acid is the proton donor and is used in the first step of the electrophilic addition mechanism. Bromide is still present, and so the second step of the mechanism would be the same as before.

One final and important note: Using clues such as how a reaction has been written is both subtle and commonly done by chemists. A phrase such as "the implied reaction appears to be…" would be quite common if you were interviewing someone about why they think one reaction is taking place rather than an alternative. This issue is present in the reaction where ethanol is used as a solvent. One quite reasonable question can be asked: At the point in the mechanism where the carbocation intermediate has been

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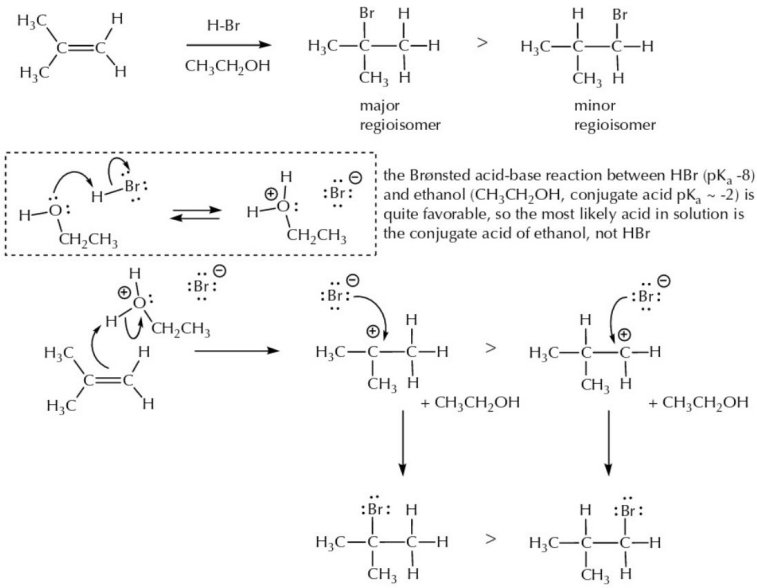
formed, bromide is not the only Brønsted base present, and it is not in the highest concentration, so why doesn't the ethanol solvent, which is also a Brønsted base, capture the carbocation? Indeed, even the pi bond from another molecule of the starting material could act as a Brønsted base.

These competitions for the carbocation are real concerns and reflect the issues that an experimentalist faces constantly when carrying out chemical reactions. Are these competitions taking place? Yes. Are these competitions creating byproducts? Yes. But if an author wants to imply a specific product, how the reaction is drawn assumes that a particular set of experimental conditions has resulted in the implied reaction as the major outcome. How to draw, speak, write, and read the implied reaction is another skill that you will develop as you continue to gain experience in your learning.

Figure 0433

Mechanism of a regioselective addition reaction with HBr in ethanol solvent.


H-Br
CH3CH2OH
major regioisomer
minor regioisomer
the Brønsted acid-base reaction between HBr (pKa -8) and ethanol (CH3CH2OH, conjugate acid pKa ~ -2) is quite favorable, so the most likely acid in solution is the conjugate acid of ethanol, not HBr
+ CH3CH2OH
+ CH3CH2OH

C. Relative Stability of Carbocation Intermediates and Their Rates of Formation

The final, unanswered question about this mechanism is the origin of the regioselectivity. What is the mechanistic basis for the Markovnikov Rule? Again, after a great deal of experimental work, the following understanding exists today: *Given the choice of different carbocation intermediates, the more stable one forms faster, and gives rise to the major product.* This statement is also the updated version of Markovnikov's

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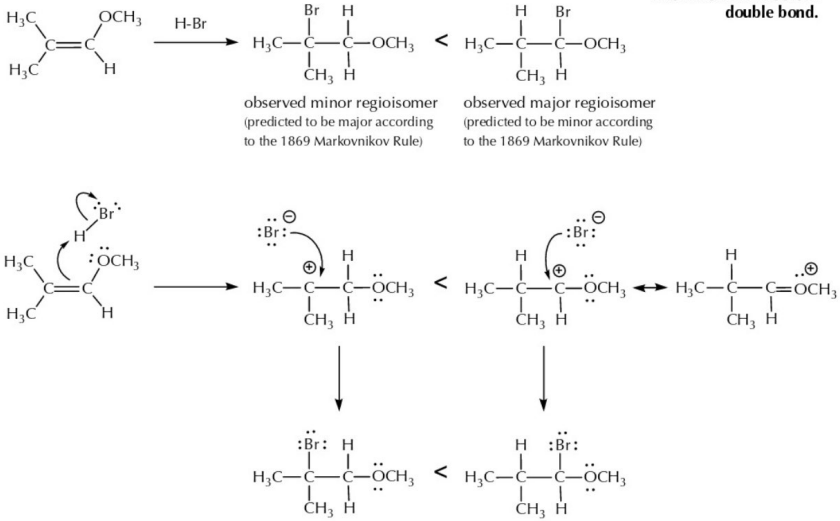
In the next example, a heteroatom-substituted double bond is used. This example demonstrates the inadequacy of the 1869 version of Markovnikov's Rule, and it provides insight into the new version of the rule, which is mechanistically based.

Using the principles of addition, the two products from the reaction shown in Figure 0434 can be predicted. And the mechanisms for how each product forms can be anticipated. Using the 1869 version of Markovnikov's Rule, the product with the two hydrogen atoms attached to the same carbon as the oxygen atom is predicted to be the major product. *It is not!* In science, when observations are made that are contrary to the prevailing rules, either the observation is wrong, or it is time to modify the rules.

Figure 0434

Mechanism of addition reaction of HBr with a heteroatom-substituted double bond.


H-Br
observed minor regioisomer
(predicted to be major according to the 1869 Markovnikov Rule)
observed major regioisomer
(predicted to be minor according to the 1869 Markovnikov Rule)

In this example, the two carbocation intermediates are significantly different because one of them has an all closed shell atom resonance contributor while the other does not. Although both of the carbocations are high-energy intermediates, the one with the closed shell resonance contributor is more stable than the other (Figure 0435). Chemists reasoned that the transition state for getting to the more stable carbocation would be lower in energy than for the less stable one, based on the idea that the factors stabilizing the carbocation (delocalization) would also be present at the transition state. This idea is an application of what is called Hammond's Postulate.

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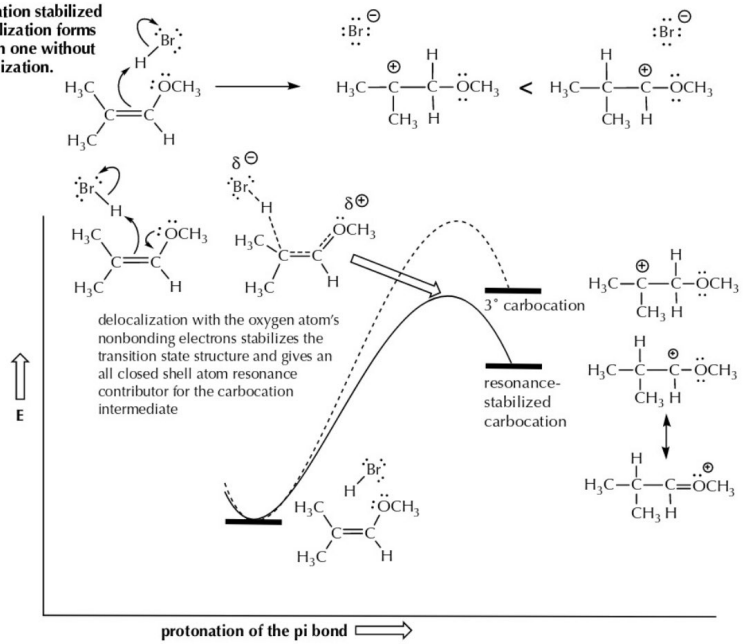
Figure 0435

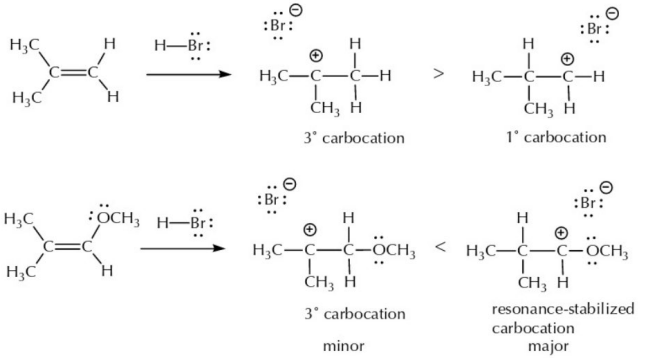
A carbocation stabilized by delocalization forms faster than one without that stabilization.


delocalization with the oxygen atom's nonbonding electrons stabilizes the transition state structure and gives an all closed shell atom resonance contributor for the carbocation intermediate
3° carbocation
resonance-stabilized carbocation
E
protonation of the pi bond

Even when delocalization with a heteroatom such as oxygen is not possible, a difference in carbocation stability is also proposed to explain the regioselectivity of the electrophilic addition reactions. Returning to an earlier example, we know there can be a structural difference between the two carbocation intermediates, namely, the degree of substitution (Figure 0436).

Figure 0436

Comparison of carbocation structures leading to different regioisomers.



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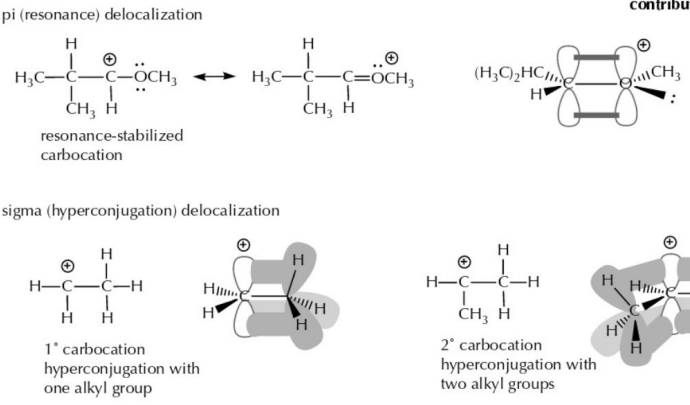
The observed major pathway, leading to the tertiary bromide, proceeds through a more substituted, tertiary carbocation, while the minor pathway, leading to the primary bromide, proceeds through a less substituted, primary carbocation. To create a coherent story about the mechanism of these reactions, the major isomer is hypothesized to arise from the more stable carbocation intermediate. In the case of heteroatom-substituted carbocations, delocalization creates resonance contributors with all closed shell atoms, and this effect is dominant when it is possible. When resonance delocalization is not possible, then the more highly substituted carbocation is more stable (forms faster, gives the major product) than the less substituted carbocation (proposed stability of carbocations: any resonance stabilization > 3° > 2° > 1°). The last question, then: How and why does degree of substitution affect carbocation stability?

After years of study, chemists have concluded that the electrons in sigma bonds can also be delocalized to a small extent, particularly when they (a) are adjacent to an empty orbital and (b) can align spatially with the empty orbital. This sigma delocalization is called hyperconjugation, and there are many observations consistent with this type of delocalization being able to provide stabilization when a sigma bond is spatially aligned with an empty orbital (Figure 0437).

Carbocations are sp^2 hybridized with trigonal planar geometries centered around an empty p orbital. When the carbocation is attached to an sp^3 alkyl group, there are adjacent CH and CC bonds sitting above and below the trigonal plane that can provide some electron overlap with the empty p orbital. The more sp^3 alkyl groups there are (3° > 2° > 1°), the more electrons are available for hyperconjugation, and the more relatively stable the carbocation will be. On the other hand, a hydrogen atom on the sp^2 open-shell carbon does not have any electron density above or below the trigonal plane and cannot provide any delocalization.

Figure 0437

A carbocation stabilized by more hyperconjugation forms faster than one with less, provided there are no resonance contributors to consider.


pi (resonance) delocalization
resonance-stabilized carbocation
sigma (hyperconjugation) delocalization
1° carbocation hyperconjugation with one alkyl group
2° carbocation hyperconjugation with two alkyl groups

Hyperconjugation (sigma delocalization) is nowhere near as stabilizing as resonance (pi delocalization), so the comparison in Figures 0435 and 0436 are important to return to, in the context of Figure 0437. The carbocation formed at the end of the double bond with the oxygen atom is significantly more stable, because of having a closed shell atom resonance contributor, than the tertiary carbocation that can form at the other end.

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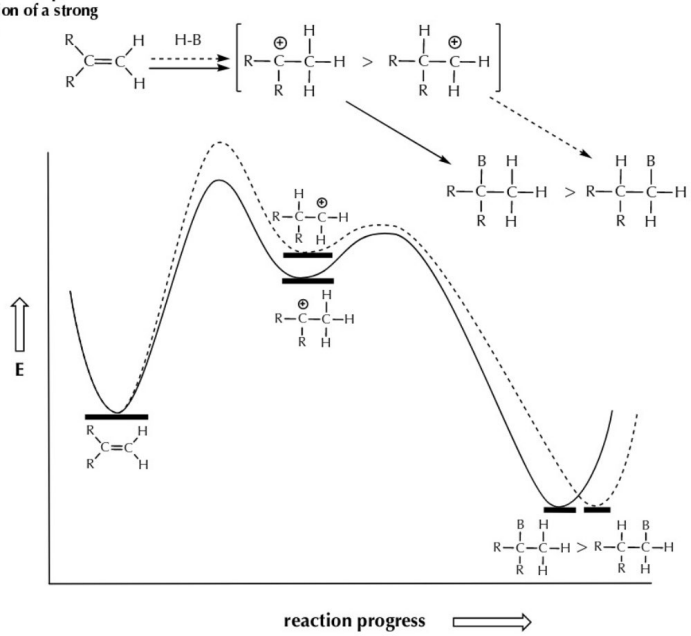
Hyperconjugation, the sigma delocalization possible for alkyl groups, is a secondary factor for evaluating carbocation stability, relative to resonance (pi) delocalization, when it is present. Thus, carbocations with resonance delocalization are more stable, regardless of the degree of substitution, than a carbocation without resonance contributors. Although resonance (pi) delocalization is more significant than hyperconjugation (sigma) delocalization, hyperconjugation is an important consideration when only the degree of substitution of a carbocation is the difference being compared.

A competition between different resonance contributors would be evaluated according to all of the normal rules for evaluating structures. And in the absence of resonance contributors, degree of substitution is used to predict carbocation stability, which follows the overall trend that resonance > 3° > 2° > 1°.

D. Energy Diagram for Electrophilic Addition of Strong Brønsted Acids

Although the specifics about a particular reaction mechanism add detail to the energy diagram presented at the beginning of this section (Figure 0422), the fundamental picture is the same (Figure 0438). As a guideline, we return to the generalization that started this section: Brønsted acids with pK_a values less than 5 can protonate pi bonds. In the first of two steps, the rate of protonation to form the more stable carbocation intermediate will be faster than the less stable one and predicts and/or explains the regioselectivity of the addition reaction. In the second step, the intermediate carbocation is captured by the conjugate base of the original strong acid.

Figure 0438
Regioselective electrophilic addition reaction of a strong Brønsted acid.



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PRACTICE QUESTIONS

4.10 For each of the following, using a generic Brønsted acid (H-B):

(i) provide the two possible protonation reaction outcomes, that is, the carbocations A and B, that result from the reaction between H-B and one pi bond

(ii) tell whether carbocations A and B are the same or different in structure, and for those that are different, whether carbocation A or B is more stable (or if they are about the same stability)

(iii) if A and B are predicted to be different in stability, explain the stability of the more stable one

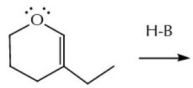
(a)

carbocation A + *carbocation B*

☐ same structures (same stability)
☐ different structures (~ same stability)
☐ different structures (A more stable)
☐ different structures (B more stable)

explain the stability of the more stable carbocation (if they are different)

(b)

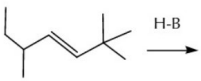


carbocation A + *carbocation B*

☐ same structures (same stability)
☐ different structures (~ same stability)
☐ different structures (A more stable)
☐ different structures (B more stable)

explain the stability of the more stable carbocation (if they are different)

(c)

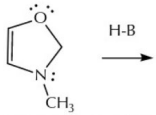


carbocation A + *carbocation B*

☐ same structures (same stability)
☐ different structures (~ same stability)
☐ different structures (A more stable)
☐ different structures (B more stable)

explain the stability of the more stable carbocation (if they are different)

(d)

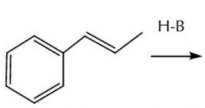


carbocation A + *carbocation B*

☐ same structures (same stability)
☐ different structures (~ same stability)
☐ different structures (A more stable)
☐ different structures (B more stable)

explain the stability of the more stable carbocation (if they are different)

(e)



carbocation A + *carbocation B*

☐ same structures (same stability)
☐ different structures (~ same stability)
☐ different structures (A more stable)
☐ different structures (B more stable)

explain the stability of the more stable carbocation (if they are different)

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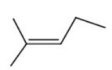
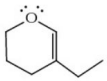
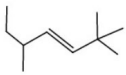
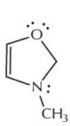
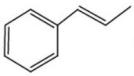
4.11 For each of the following, provide the two electrophilic addition reaction products. Using the modern version of Markovnikov's Rule (in the mechanism, the more stable carbocation forms faster), circle the expected regioselectivity of the reaction in the box between the two regioisomers (>, <, or about the same).

(a)  H-Br → | regioselectivity > < about the same |

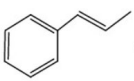
(b)  H-Cl → | regioselectivity > < about the same |

(c)  H-Br → | regioselectivity > < about the same |

(d)  → | regioselectivity > < about the same |

(e)  H-Cl, CH_3OH → | regioselectivity > < about the same |

4.12 Provide the complete, stepwise, curved arrow mechanism for the formation of the major product in the following electrophilic addition reaction. Be sure to include the Brønsted acid that is present in highest concentration and its mechanism of formation, also.

 H-Cl, CH_3OH → major product

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PRACTICE QUESTIONS

4.10 For each of the following, using a generic Brønsted acid (H-B):

(i) provide the two possible protonation reaction outcomes, that is, the carbocations A and B, that result from the reaction between H-B and one pi bond

(ii) tell whether carbocations A and B are the same or different in structure, and for those that are different, whether carbocation A or B is more stable (or if they are about the same stability)

(iii) if A and B are predicted to be different in stability, explain the stability of the more stable one

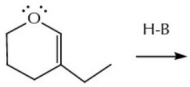
(a)

carbocation A + carbocation B

same structures (same stability) ☐
different structures (~ same stability) ☐
different structures (A more stable) ☐
different structures (B more stable) ☐

explain the stability of the more stable carbocation (if they are different)

(b)



carbocation A + carbocation B

same structures (same stability) ☐
different structures (~ same stability) ☐
different structures (A more stable) ☐
different structures (B more stable) ☐

explain the stability of the more stable carbocation (if they are different)

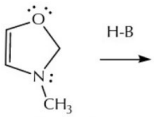
(c)

carbocation A + carbocation B

same structures (same stability) ☐
different structures (~ same stability) ☐
different structures (A more stable) ☐
different structures (B more stable) ☐

explain the stability of the more stable carbocation (if they are different)

(d)

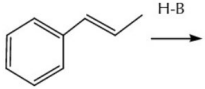


carbocation A + carbocation B

same structures (same stability) ☐
different structures (~ same stability) ☐
different structures (A more stable) ☐
different structures (B more stable) ☐

explain the stability of the more stable carbocation (if they are different)

(e)



carbocation A + carbocation B

same structures (same stability) ☐
different structures (~ same stability) ☐
different structures (A more stable) ☐
different structures (B more stable) ☐

explain the stability of the more stable carbocation (if they are different)

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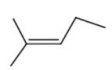
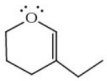
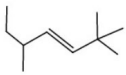
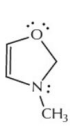
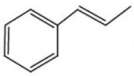
4.11 For each of the following, provide the two electrophilic addition reaction products. Using the modern version of Markovnikov's Rule (in the mechanism, the more stable carbocation forms faster), circle the expected regioselectivity of the reaction in the box between the two regioisomers (>, <, or about the same).

(a)  H-Br → | regioselectivity > < about the same |

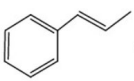
(b)  H-Cl → | regioselectivity > < about the same |

(c)  H-Br → | regioselectivity > < about the same |

(d)  → | regioselectivity > < about the same |

(e)  H-Cl, CH_3OH → | regioselectivity > < about the same |

4.12 Provide the complete, stepwise, curved arrow mechanism for the formation of the major product in the following electrophilic addition reaction. Be sure to include the Brønsted acid that is present in highest concentration and its mechanism of formation, also.

 H-Cl, CH_3OH → major product

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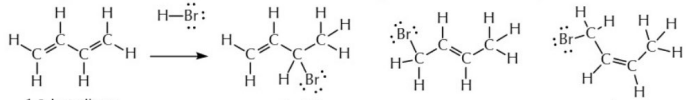
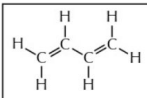
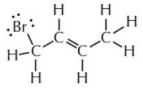
4.13 The electrophilic addition reaction of HBr to 1,3-butadiene gives a mixture of three products:



1,3-butadiene | product **P** | product **Q** | product **R**

(a) Provide the complete, stepwise, curved arrow mechanism for the formation of product **Q**.





product **Q**

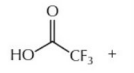
(b) Draw the transition state structures for the first step in your mechanism from part (a), and also from the last step. Use dotted lines for partial bonds and indicate partial charges as necessary.

transition state structure for the first step

transition state structure for the last step

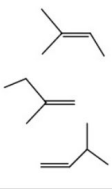
(c) Which of the three products (**P**, **Q**, or **R**) is predicted to be the major regiosiomer according to Markovnikov's Rule? Explain why, using words and drawings.

4.14 The rate of electrophilic addition of trifluoroacetic acid with one of these three C_5H_{10} double bond isomers is observed to be 60,000 times slower than the other two. Which one is the slow one? Why is it slower? Draw the structure of the major regioisomer expected to form in the reaction of the slow isomer.



trifluoroacetic acid

circle the slow one



major regioisomer from the slow one

why is the slow one slowest?

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4.4 Electrophilic Addition Reactions of Weak Brønsted Acids

A. Observed Outcomes: The Need for a Strong Acid Catalyst

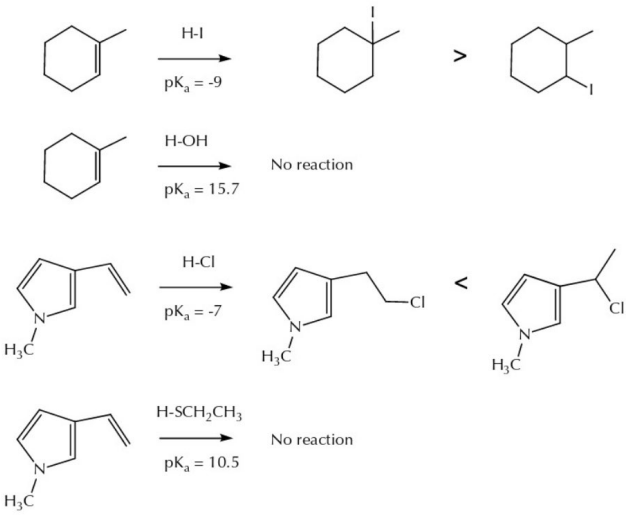
The first step of the electrophilic addition mechanism of Brønsted acids is protonation of a pi bond, and there is an experimentally determined threshold value for the strength of an acid that can be predicted to carry out this reaction, and a pK_a above which the protonation reaction is not favorable. Although there is no reason for a clean line of demarcation, the common value of $pK_a = 5$ is used as a guideline. Naturally, there may be acids above this value that are observed to participate in the reaction, and there may be those below the value that do not. And there may be pi binds that are more or less reactive in ways that influences the strength of the acids they react with. The threshold of $pK_a = 5$ for Brønsted acids that can predictably protonate pi bonds is a general guideline that can be used without other experimental information or guidance.

Quite emphatically: *No predictive model is perfect. When experimental information contradicts any general guideline, then you always follow the experimental results.*

Weaker Brønsted acids ($pK_a > 5$) are typically not strong enough to protonate a pi bond, and so the addition reaction is not observed upon simply mixing the two reagents together (Figure 0439).

Figure 0439

Addition reactions of weak Brønsted acids are not observed under the same reaction conditions as strong Brønsted acids.



The most common experimental strategies for trying to get a slow or sluggish reaction to proceed are (a) raising the temperature, (b) increasing the concentration, (c) changing the solvent, and (d) finding a catalyst.

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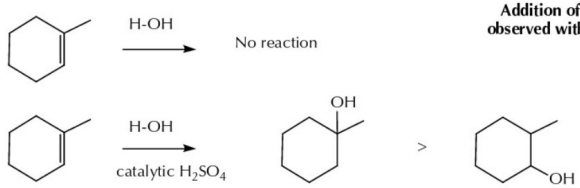
The addition reactions of weak Brønsted acids (pK_a range ~ 5–18) to pi bonds is observed when a strong acid catalyst is added to the reaction (Figure 0440). Note that all of the observed features of these additions follow those shown in the previous section: (1) addition of a Brønsted acid (H-B) occurs with a pi bond, making a new CH bond and a new CB bond, and (2) the regioselectivity follows the modern Markovnikov Rule: the CH bond forms on the end which is consistent with a protonation that leaves the more stable carbocation intermediate.

Figure 0440

Addition of weak Brønsted acids is observed with a strong acid catalyst.



Note how powerful the analogy is between the weak and strong acid reactions. The overall transformations are identical, as are the predictions about the regioselectivity. From a connectivity standpoint, the reactions of strong and weak acids give the same outcome. The place where they differ is in the reaction conditions (the need for a strong acid catalyst) and so in the detailed explanation (the mechanism) for how the acid catalyst functions.

B. Proposed Stepwise Mechanism: A Catalytic Cycle

The mechanism for the acid-catalyzed addition of weak Brønsted acids to pi bonds requires three mechanistic steps rather than the two steps needed in the addition reaction of strong acids. The general statement for this reaction mechanism:

The addition reaction of weak Brønsted acids (HB; pKa ~5-18) to pi bonds (C=C) is observed with a strong acid catalyst (e.g., inorganic acids such as sulfuric acid, nitric acid, and phosphoric acid, or strong organic acids). The reaction mechanism takes place in three steps.

> *In the first, rate-determining step, the pi bond is protonated by the strongest Brønsted acid in solution, the conjugate acid of the original weak acid, to give the new C-H bond at one end of the double bond and a carbocation at the other end (Markovnikov regioselectivity).*
>
> *In the second step, the high-energy carbocation intermediate is rapidly captured by the original, weak Brønsted acid, acting as a Lewis base, to form a cationic intermediate, making the CB bond as the conjugate acid of the product.*
>
> *In the last step, deprotonation of the cationic intermediate gives the final addition reaction product.*

The description of the first step reveals the role of the acid catalyst. Some of the weak Brønsted acid is converted into its conjugate acid, which takes an acid with a pK_a greater than 5 and transforms it into an acid whose pKa is less than 5, and therefore capable of protonating a pi bond. Although the acid catalyst ($pK_a < 5$) is perfectly capable of protonating a pi bond, the experimental reality is that the protonation of the original weak acid will happen much faster and more favorably than the reaction with the pi bond, as in the case of using a reactive solvent in the strong acid addition case at the end of Section 4.3B.

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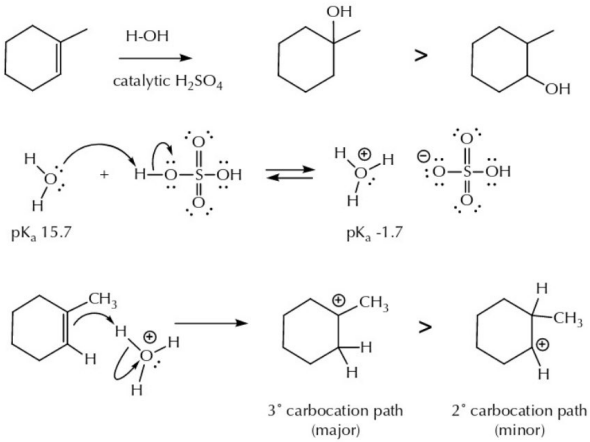
Once the conjugate acid of the original weak acid is formed, the first step in the addition reaction is identical to that of the strong acid case because this conjugate acid has a $pK_a < 5$ (Figure 0441).

Figure 0441

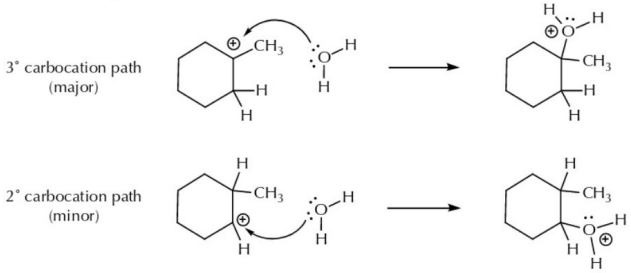
Protonation by an acid catalyst gives the conjugate acid of an originally weak acid, which is able to protonate a pi bond to give a carbocation intermediate.



The second step of the weak acid addition reaction is conceptually the same as in the strong acid addition. A Lewis acid-base reaction takes place in which the carbocation intermediate is captured by the conjugate base of the acid that did the protonation in the first step. The difference from the strong acid case is that in the first step here, the conjugate acid of the original weak acid was the proton source, and so its conjugate base is the original weak acid (Figure 0442).

Figure 0442

Capture of the carbocation intermediate by the original weak acid gives the conjugate acid of the expected addition reaction product.



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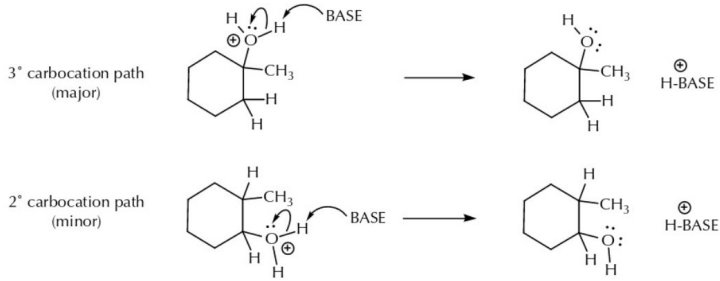
When the carbocation is captured by the original weak acid, the reaction mechanism is not yet complete. This cationic intermediate is the conjugate acid of the expected addition reaction product, and so one more step is needed: to deprotonate this intermediate. Figure 0443 shows this deprotonation reaction using the word "BASE" as a placeholder for the identity of the base that carries out this third step.

Figure 0443

Deprotonation by a base is the third step in the acid-catalyzed addition reaction of a weak acid with pi bonds.

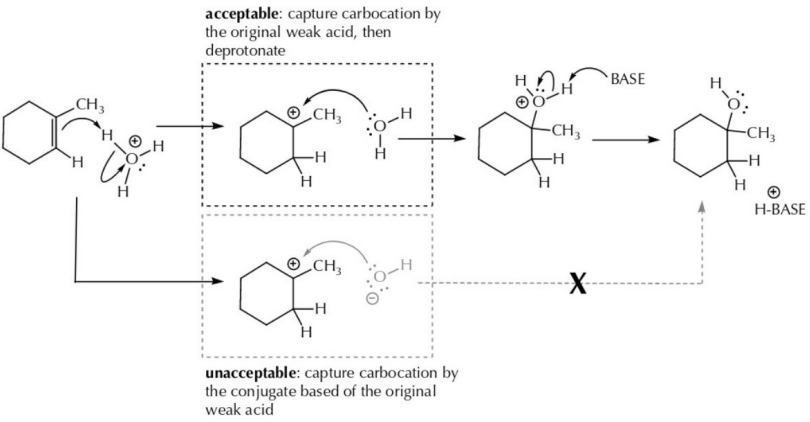


The product from the addition of water contains a hydroxyl group. The two most common questions that learners have about this weak acid case are (1) why is the third step needed, why not just capture the carbocation with hydroxide, the conjugate base of water, which was the original weak acid? And (2) what is the identity of the base used in the third step?

The first question is easier to answer than the second one: There is simply no significant concentration of hydroxide in this reaction (Figure 0444). Hydroxide, the conjugate base of the original weak acid, water,

Figure 0444

Capturing the intermediate carbocation by the conjugate base of a weak acid is impossible because the conjugate base does not exist under acidic conditions.


acceptable: capture carbocation by the original weak acid, then deprotonate
BASE
H-BASE
X
unacceptable: capture carbocation by the conjugate based of the original weak acid

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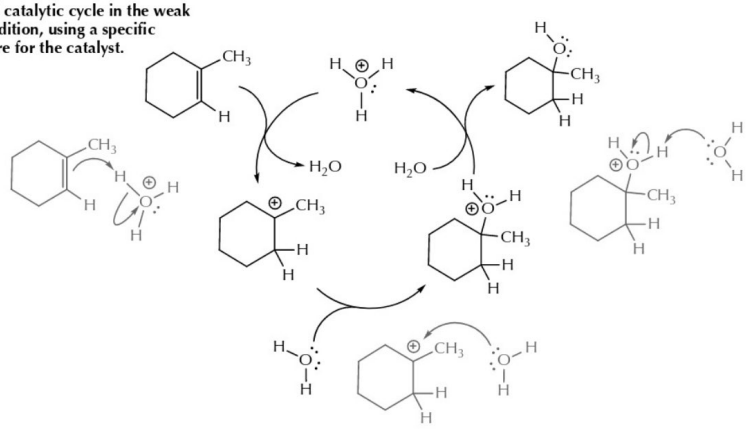
is a strong base, and there is none of it present under acidic conditions. This point is important, because it speaks to how experimental reality is the underlying feature of science. Writing the capture of the carbocation by the conjugate base of the original weak acid, in this case hydroxide ion, is perhaps the most common error made when learning this topic because the process looks so reasonable. Unfortunately, it is also a completely nonsensical fiction because that conjugate base does not exist to any significant degree under these acidic conditions: Proposing the existence of a strong base to carry out any reaction in the presence of a strong acid, other than a fast acid-base reaction, goes against the principles of acid-base chemistry. This principle is exactly the one that requires the reaction between the acid catalyst and the original weak acid, in the first place. This lesson is critical: A mechanism is not just any story you want to tell; it needs to be rational and consistent with chemical principles and experimental reality.

Answering the second question (what is the identity of the base in the last step?) is harder because it is quite difficult to determine, experimentally, the identity of the base that does the deprotonation in the third mechanistic step of this reaction. One useful convention is that catalyzed reactions should always be able to show a catalytic cycle. That is, because a catalyst is used and then reused, the molecular structure of the catalyst as it enters the reaction needs to be accompanied by a step that regenerates that structure, exactly, as it exits the reaction. This enter-and-exit requirement defines what it means to be a catalyst and is why these are referred to as cycles.

In the addition reaction example used above, hydronium ion (the conjugate acid of the original weak acid) is proposed as the catalyst in the addition reaction mechanism that protonates the pi bond in the first step. Given how few different molecules are in this reaction mixture, one rational base to use to deprotonate the cationic intermediate in the third step—and regenerate the hydronium ion catalyst—is another molecule of the original weak acid, water. Experimentally, there are plenty of those water molecules around, as it is likely the weak acid is used in excess, and perhaps even as the solvent for the reaction. Figure 0445 shows the full catalytic cycle using the hydronium ion as the catalyst, which appears at the top of the cycle. These cyclic schemes are commonly used in catalysis reactions to show how the single molecule of catalyst is used and re-formed as the transformation of starting material to product takes place.

Figure 0445

The full catalytic cycle in the weak acid addition, using a specific structure for the catalyst.



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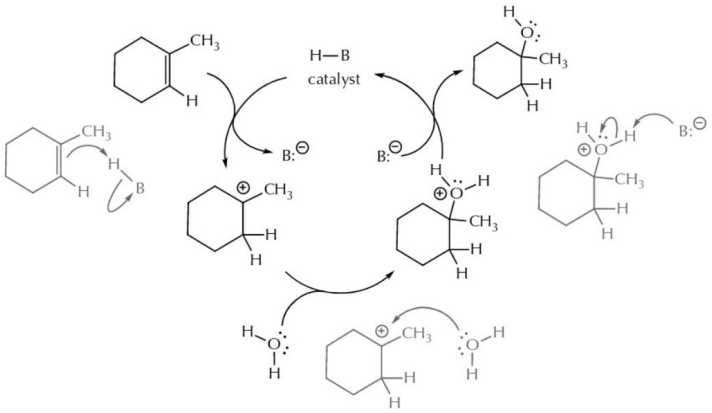
As stated, the exact identity of the base, and also the actual acid catalyst, can be hypothesized, but their identities are experimentally difficult to determine. In the vast majority of cases, their identities are also irrelevant, and it is quite common to see chemists use generic representations for the identity of the acid catalyst (H-B or H-B$^+$) and its conjugate base (B:- or B:), when drawing mechanisms. The reaction cycle from Figure 0445 is re-represented in Figure 0446 using the generic representation.

Figure 0446

The full catalytic cycle in the weak acid addition, using a generic representation for the catalyst.



The presentations about these acid-catalyzed reactions are a great place to remind you about Section 3.2C (Are There Free Protons in a Reaction Flask? The Lewis Versus Brønsted Acid Debate).

In this text, we are following a convention for drawing mechanisms which acknowledges that proton transfer steps are as important as any other step, that the proton source should be a molecule (and not a free proton), and that a base is needed to deprotonate a molecule (rather than a proton simply falling off).

Be warned that other authors, texts, and online resources will not always follow the convention we are using here, and so you may need to translate what you find in other places. A strong argument can be made for not ignoring and/or abbreviating steps when drawing a mechanism, as a mechanism is meant to represent the complete, stepwise story for how a reaction takes place. For your information, Figure 0447 on the next page shows a few examples for representing proton transfer reaction mechanisms that are acceptable and unacceptable.

C. Energy Diagram for Electrophilic Addition of Weak Brønsted Acids

As a general guideline, the conjugate acids of Brønsted acids with pK_a values between about 5 and 18, whose pK_a values all drop below 5, can protonate pi bonds. The first of two steps are then comparable to the strong acid additions: The rate of protonation to form the more stable carbocation intermediate will be faster than the less stable one and predicts and/or explains the regioselectivity of the addition reaction. In the second step, the intermediate carbocation is also captured by the original weak acid, acting as a Brønsted base, forming an intermediate that is then deprotonated to give the addition reaction product.

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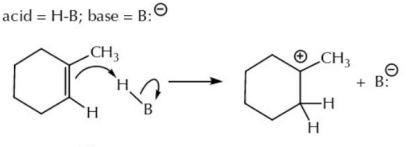
Figure 0447

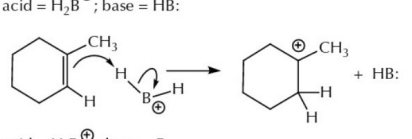
Acceptable and unacceptable representations for proton transfer mechanisms.

acceptable mechanisms (using generic acids and bases):

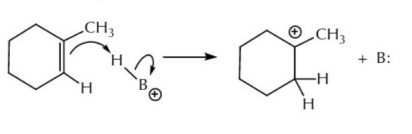
acid = H-B; base = B:⊖



acid = $H_2B^{\oplus}$; base = HB:



acid = H-B$^{\oplus}$; base = B:



unacceptable mechanisms (loss/gain of free protons, H^+ and missing curved arrows)

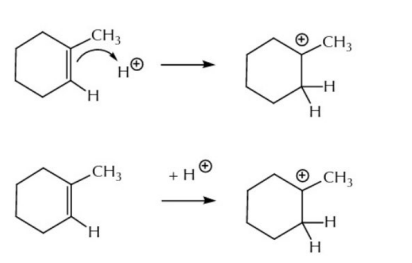


Figure 0448 shows the energy diagram that compares the full, three-step mechanism for the two regioisomers derived from the addition of a weak Brønsted acid to an unsymmetrical double bond under acid-catalyzed conditions. Of particular importance is a reminder that the regioselectivity is established in the first, protonation step, where the rate for forming the 3° carbocation intermediate is faster (lower activation energy) than that for forming the 1° carbocation (higher activation energy). The other two steps (carbocation capture and deprotonation of that intermediate) are fast and nearly energetically identical.

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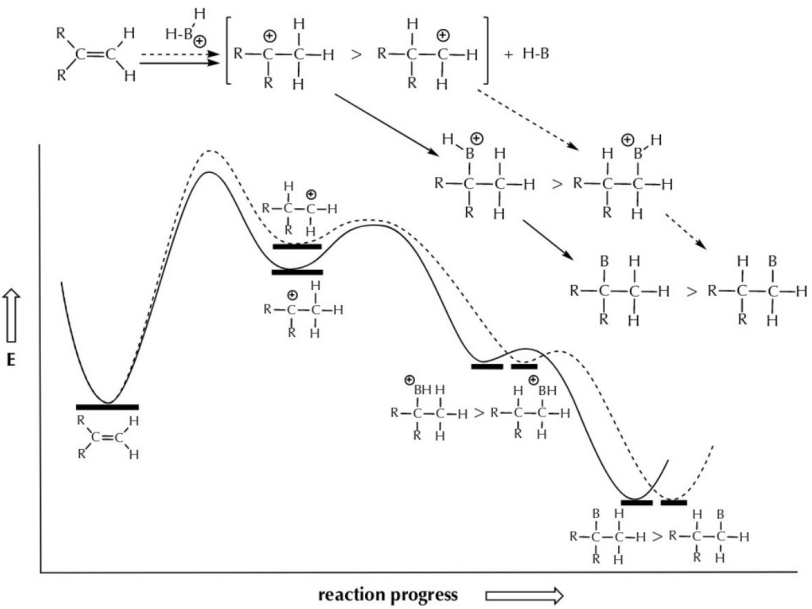
Figure 0448

Regioselective electrophilic addition reaction of a weak Brønsted acid.



D. Extending Electrophilic Addition to Other Nucleophiles and Electrophiles

The two pi bonds in carbon-carbon triple bonds can undergo electrophilic addition reactions of strong and weak acids with all the same features as the reactions of double bonds. The pK_a threshold of about 5 operates, as does Markovnikov's Rule (the more stable carbocation is formed faster) for predicting regioselectivity (or lack thereof).

Because a triple bond has two pi bonds, a critical piece of experimental information is needed: Is the reaction being performed in a way where one or two addition reactions are expected? With addition reactions of triple bonds, then, the writer or speaker needs to give some indication about the stoichiometry of the reaction. Ways to indicate the stoichiometry include the inclusion of "1 equivalent," or "2 equivalents," or "excess" with the reagent that is adding, or perhaps indicating a "1:1 molar ratio" or "1:2 molar ratio." Another indicator might be an experimental result, such as the molecular formula of the product, which would indicate whether one or both of the pi bonds underwent addition. Some examples of addition reactions involving triple bonds are given in Figure 0449, as well as the application of the electrophilic addition reaction mechanism to one of these examples, in Figure 0450 (both shown on the next two pages).

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As the chapter ends, think back to the power of analogies that was discussed in the opening essay for Chapter 3. The specifics of any given organic chemical reaction might look incredibly different from the exact examples you have seen before, but the fundamental types of reactions and the ability to build analogies are exceptionally powerful tools. This power to understand new and unfamiliar observations is exemplified here at the end of this chapter that introduced electrophilic addition reactions. Above, you can see how addition reactions of carbon-carbon triple bonds, as a different nucleophile, relate to those of carbon-carbon double bonds. And below, there is an extension of what can serve as the electrophile.

Figure 0449

Examples of addition reactions of triple bonds.

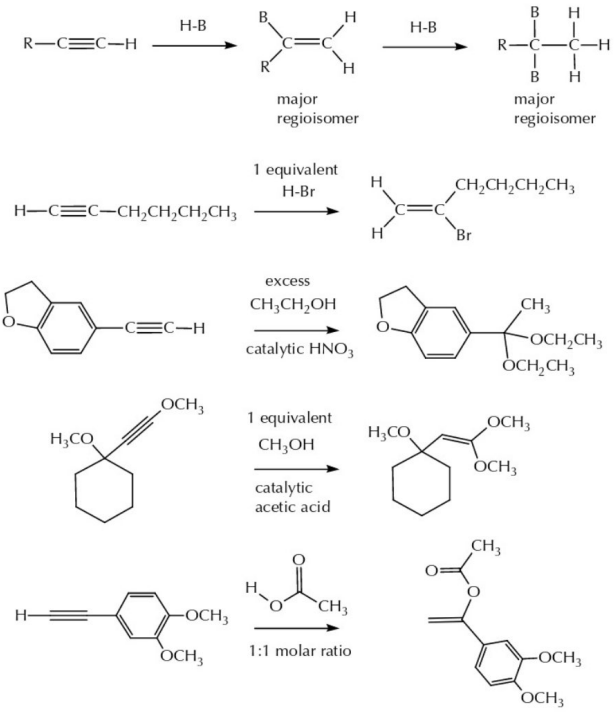

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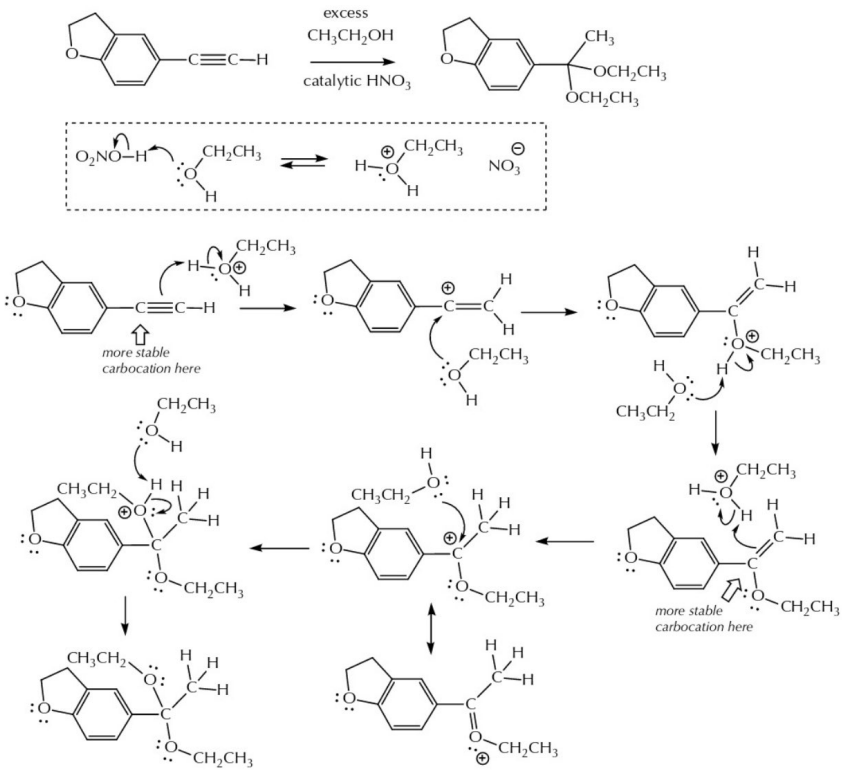
Figure 0450

Applying the electrophilic addition reaction mechanism to a triple bond.



An extension on the electrophilic addition mechanism. Protonation reactions are not the only source of electrophiles for these electrophilic addition reactions that occur through carbocation intermediates. Figure 0451 (on the next page) presents an unfamiliar experimental observation. As you work from top to bottom in this figure, you will see how an experienced organic chemist might break down the observation by classifying the reaction in familiar terms, first as an addition, and then the application of the electrophilic addition reaction as an analogy. At this point in your experience, you should not be able to invent this analysis, but you should be able to understand its logic.

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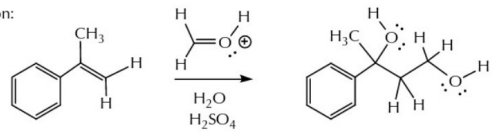
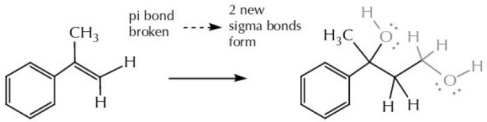
Figure 0451

Applying the electrophilic addition reaction mechanism to a new electrophile.

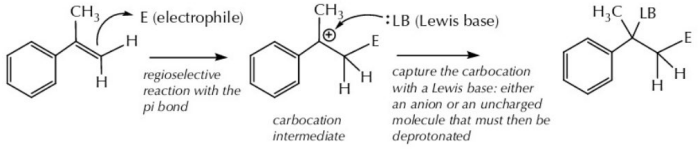
observed reaction:



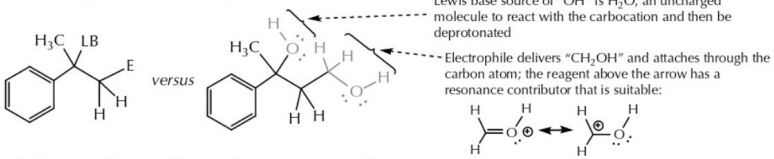
classify the reaction as addition by comparison between starting material and product:



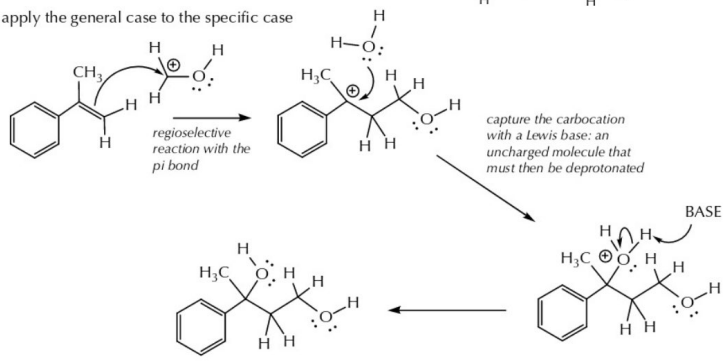
think about the analogies that can be made (right now, you only have electrophilic addition)


E (electrophile)
regioselective reaction with the pi bond
carbocation intermediate
LB (Lewis base)
capture the carbocation with a Lewis base: either an anion or an uncharged molecule that must then be deprotonated

compare the general idea to the specific case


versus
Lewis base source of "OH" is H_2O, an uncharged molecule to react with the carbocation and then be deprotonated
Electrophile delivers "CH_2OH" and attaches through the carbon atom; the reagent above the arrow has a resonance contributor that is suitable:

apply the general case to the specific case


regioselective reaction with the pi bond
capture the carbocation with a Lewis base: an uncharged molecule that must then be deprotonated
BASE

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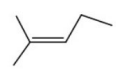
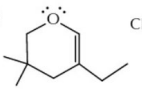
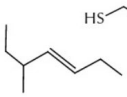
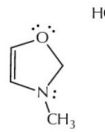
PRACTICE QUESTIONS

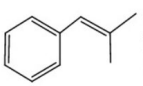
4.15 For each of the following, provide the two electrophilic addition reaction products. Using the modern version of Markovnikov's Rule (in the mechanism, the more stable carbocation forms faster), circle the expected regioselectivity of the reaction in the box between the two regioisomers (>, <, or about the same).

(a) 

(b) 

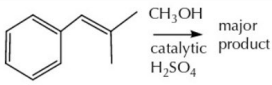
(c) 

(d) 

(e) 

	regioselectivity > < about the same		*regioselectivity* > < about the same
	regioselectivity > < about the same		*regioselectivity* > < about the same
	regioselectivity > < about the same		*regioselectivity* > < about the same
	regioselectivity > < about the same		*regioselectivity* > < about the same
	regioselectivity > < about the same		*regioselectivity* > < about the same

4.16 Provide the complete, stepwise, curved arrow mechanism for the formation of the major product in the following electrophilic addition reaction. Be sure to include the most likely Brønsted acid that is present and its mechanism of formation. Assume a catalytic cycle where the acid used in the first step is regenerated in the last step.



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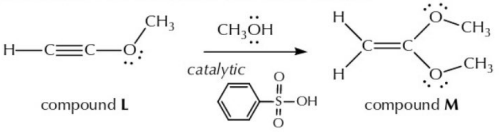
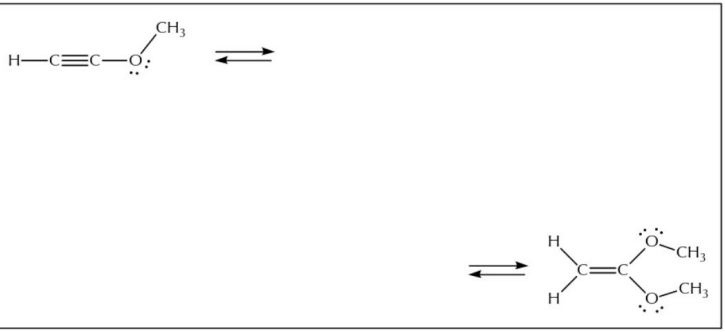
4.17 The electrophilic addition reaction of 1-methoxyethyne (compound **L**) with methanol (CH_3OH) in the presence of catalytic sulfuric acid gives 1,1-dimethoxyethene (compound **M**).



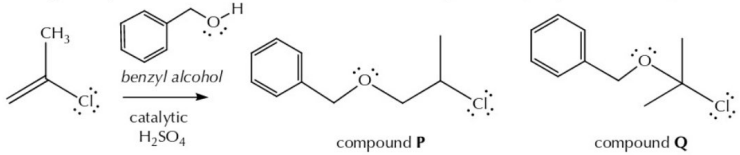
compound **L** compound **M**

(a) Mechanistically, the acid catalyst that participates directly in this reaction is not the molecule shown under the arrow in this equation (an organic acid with a pK_a value of -1). What is the structure of the acid that is present in solution when a small amount of this organic acid is added to a large excess of methanol.

(b) Provide the complete, stepwise, curved arrow mechanism for the transformation of compound **L** to compound **M**. Use the generic "H-B" for any Brønsted acid you need, and $B^{\ominus}$ for its conjugate base.



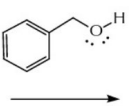
4.18 The following electrophilic addition reaction results in a mixture of regioisomers (compounds **P** and **Q**).



compound **P** compound **Q**

(a) Either **P** or **Q** is the major regioisomer, and the other is minor. Provide the structure for the single most important intermediate that is used to explain the regioselectivity, that is, why the major regioisomer is favored. Show the most significant resonance contributor of this intermediate, which leads to the major product.

(b) In the next step, the intermediate reacts with the benzyl alcohol. Show the curved arrow mechanism for the reaction between benzyl alcohol and this most significant resonance contributor you have drawn in part (a).



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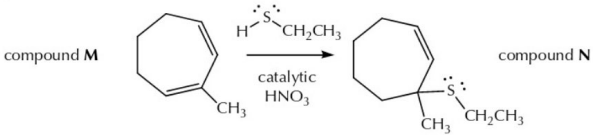
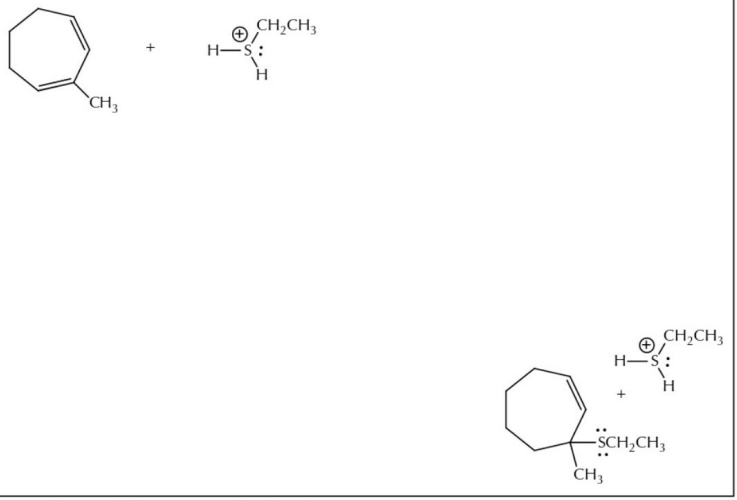
4.19 Thiols (such as ethanethiol, CH_3CH_2SH) participate in many reactions that are analogous to their alcohol counterparts (such as ethanol, CH_3CH_2OH). The electrophilic addition reaction of ethanethiol to compound **M** gives compound **N** with a high degree of regioselectivity. Because ethanethiol is a relatively weak acid ($pK_a = 10.5$), a strong acid catalyst is required.



(a) Provide the complete, stepwise curved arrow mechanism for this reaction (including nonbonding electrons). The most likely acid present in this reaction is the conjugate acid of ethanethiol ($CH_3CH_2SH_2^+$) which, as a true catalyst, is consumed in the first step and reformed in the last step.



(b) There are four possible protonation sites for the first step, yet the rate of the reaction for the one that gives this product is significantly faster than the other three. Using words and a drawing, provide a complete explanation for why the observed protonation is fastest.

(c) Which of the other three protonations is the next fastest? Draw it and provide an explanation for your selection.

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Reflections About Science: Classification as a Diagnosis Before You Select a Treatment

Tens of thousands of students spread across thousands of classrooms wonder what they might get from learning organic chemistry that will serve them in the future. It is an excellent question that should be asked, and answered, by all courses. For some, the answer will include practical reasons: My program required it, I need to take it as a prerequisite for biochemistry, and so on. Returning to the essay on Transformational Teaching in Chapter 2, there is also a lesson to be found in learning-related values, that is, lessons that come along with learning the subject matter that will endure long past the details of mechanisms and pK_a values.

This chapter has emphasized how classification is needed in learning organic chemistry. If you decide that a reaction is an electrophilic addition reaction of a strong acid when it is really a weak acid, you can then operate on the information and show the strong acid pathway correctly, but the response will be incorrect because the first decision was incorrect. Classification relates to decision-making, how to gather and balance information and then take to an action.

If you are travelling along a sidewalk and come to a traffic intersection, you have a simple choice to make: cross the road, or do not cross the road. Both are perfectly reasonable decisions. But the way you know which one to make is not at all random. Your decision (an action, a treatment to the question of "whether to cross the road?") is predicated by a diagnosis (is it safe to cross the road?).

If every decision you make is a choice between options, then a diagnosis process precedes every choice. Like it or not. Diagnoses are classifications (are the conditions safe or unsafe?) based on evidence and criteria. Because both of your options are reasonable (to cross or not to cross), the only way to sort them out is through an accurate diagnosis.

Clearly, in this little example, if your diagnosis is wrong (it is safe to cross, when it is not), then the treatment (crossing) could be a real problem! And not because you do not know how to cross the road, but because you are doing it at the wrong time.

This distinction between diagnosis and treatment plays out in hundreds of different ways. If you see "2 x 3" and misdiagnose this as an addition question, you can perfectly well apply the treatment of addition (answering "5") and be quite confused by being told you are incorrect. You have not misunderstood multiplication… you did not know you needed to do multiplication. You have confidently and correctly carried out an additional treatment, but like crossing the road at the wrong time, you end up getting hit by the traffic.

Even worse, the question might have been "3.5 x 1.4." It is not worse because this is a slightly more complex question, but because your misdiagnosis of multiplication for addition gives an answer of "4.9," which turns out to be exactly the same as the result from multiplication! You will get the answer correct for a completely incorrect reason (in other words, you made it across the busy intersection without getting hit, but it was just blind luck). Unless you study the process of how you produce an answer, two people might be using totally different rules and completely disagree, even though they produce the same (literal) answer.

Learning chemistry (and a bunch of other things… in fact, likely everything) works the same way. We humans deal with large amounts of information by organizing stuff into categories, then subcategorizing those categories, and so on, as a way to not have to be thinking about everything at once. If you see a new reaction that you need to propose a mechanism for, then classifying it as addition versus substitution versus elimination is a critical first step. If you do the diagnosis step incorrectly, it really does not matter

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what else you do that is correct, because (except for wild coincidences) the answer will be wrong. You might correctly identify a reaction as an addition of a Brønsted acid. Then you need to correctly subclassify it as a strong versus a weak acid, according to the criteria in this chapter, to be able to draw the proper mechanism. If you misdiagnose the question as a strong acid (when it is actually weak), you can draw the two-step mechanism as applied to the weak acid perfectly correctly, but it is nonetheless completely wrong. Not because your application of the details was wrong, but because you picked the wrong ones to apply.

After all, if a physician diagnoses a patient with a broken leg when the problem is actually a case of the measles, it really does not matter how well the leg gets set. Once the diagnosis is wrong, all the skill at implementing a treatment becomes meaningless because the wrong one is being implemented.

One of the most common behaviors observed in expert problem solvers is the time they take with diagnosis and trying to get it right. Taking the time to stand back from the information to put all the pieces together is an incredibly important skill. By the time you are implementing a solution, you want to be as confident as possible that you know what the question was about, and that you have conceptualized your solution before you start acting upon it—knowing that it is safe to cross the road before you start to move, rather than thinking about it halfway through the intersection.

Novice learners, in contrast, tend to react to the first thing they recognize, and they want to get moving on producing an answer too quickly, even though they might find themselves in the middle of a busy intersection and unable to start over. Again, you can have all of the details under control, but if you have not figured out what needs to be used, and when, your understanding is simply incomplete.

You might think that the questions that come after each section of a book are somehow easier than the ones at the end of a chapter, which are easier still than the ones you see on an examination. They are not. The difference is how much of the diagnosis is being done for you. At the end of a section, you not only have fewer choices to make, but you know before you look at the question what area(s) it is going to cover. The section on the addition of weak acids had questions about the addition of weak acids; you did not need to make that decision. At the end of the chapter, the treatments are the same, but the diagnosis is now more complex.

You must make a diagnosis (to cross or not to cross) before you take an action; like it or not, it is unavoidable. And within an academic subject, and then with a profession, the diagnoses get more and more complex, with increasing criteria that are also more nuanced in their distinctions.

In an introductory survey course, the need for diagnosis is often strongly signaled for you. Sometimes the choice is obvious: An electrochemistry question is difficult to confuse with a gas law question. Or perhaps the diagnosis is actually made for you, and the questions carry labels (these are "stoichiometry" questions, and these are "equilibrium" questions). Introductory survey classes are often described as being "a mile wide and an inch deep" because there is so much breadth of coverage but little depth. The actual demand for sophisticated diagnosis in that sort of course is different than one in which the information is highly hierarchically organized.

This chapter is a strong preview of the need for you to start to focus on developing good diagnosis skills, in addition to treatment skills, for understanding organic chemistry. The distinction is important to master, anyhow, because as you continue to specialize in your education (and then in your profession) you will not only have to develop the ability to deal with information, but also how people have organized it. It is as inevitable as it is necessary, or you are likely to find yourself caught in the middle of an intersection, wishing you had spent just a moment more deciding whether or not you should have stepped out into the traffic.

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Summary

This chapter has introduced three different aspects of how classifications of information will play out in learning organic chemistry.

First, there are four fundamental categories of bonding changes: complexation/decomplexation (the bond forming and breaking process between Lewis acids and bases), substitution (the sigma bond to sigma bond exchange), addition (breaking a pi bond to give two new sigma bonds), and its reverse, elimination. As conceptual relationships, these classifications (if known) can be applied to vast numbers of unfamiliar organic chemical reactions.

Second, moving fluidly between representational forms enhances the meaning of these different categories. Communicating with chemical structures is only part of the story. Text and vocabulary, such as the subcategorization of structures by the "degree of substitution" terminology, allows for more subtle distinctions with categories such as "double bonds" or "alkyl halides" by identifying similar properties or similar reactivities. Structural drawing and text also need to meld seamlessly with graphical representations, such as energy diagrams, which summarize relationships that are not easy to do with drawings and text alone. Energy diagrams, in particular, capture the story of a reaction mechanism by combining relative energies and relative rates along with structural information.

Third, the difference in the electrophilic addition reactions of strong and weak Brønsted acids to pi bonds introduces two case studies about multistep mechanisms where the difference in classification of one factor (strong versus weak acid) does not influence the overall outcome (both are additions) but rather is in the details of how the outcome arises.

The addition of strong Brønsted acids ($pK_a < 5$) to pi bonds takes place in two steps. (1) The pi bond is protonated by the most likely Brønsted acid present, according to the Markovnikov Rule about regioselectivity, to form the more stable carbocation intermediate at a faster rate than the less stable one; and (2) the carbocation intermediate is then captured by the conjugate base of the acid to complete the addition reaction.

The addition of weak Brønsted acids (pK_a ~5–18) to pi bonds is catalyzed by strong acids and takes place in three steps. (1) The pi bond is protonated by the most likely Brønsted acid present, which is the conjugate acid of the weak acid, according to the Markovnikov Rule about regioselectivity, to form the more stable carbocation intermediate at a faster rate than the less stable one; (2) the carbocation intermediate is then captured by the original weak acid before (3) the resulting cationic intermediate is deprotonated to complete the addition reaction.

Finally, this chapter provides a strong preview of your need to develop strong diagnosis (classification) skills for undertaking the study of organic chemistry reactions. If you did not read the preceding "Reflections on Science" essay, it provides good advice that many students have found valuable in how to approach learning.

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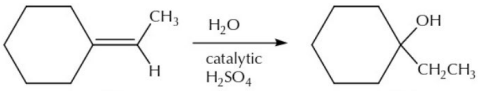
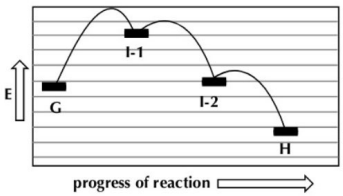
CHAPTER QUESTIONS

4.20 The electrophilic addition of water to compound **G** using an acid catalyst results in the product shown here (compound **H**) as the major regioisomer.



compound **G** compound **H**

The energy diagram for this multistep mechanism is shown to the right. The initial point represents the compound **G**, which first combines with H_3O^+ (the conjugate acid of water, formed in the reaction between water and sulfuric acid) to give intermediate **I-1**, which then goes on to form intermediate **I-2**, which finally proceeds to the product, compound **H**).

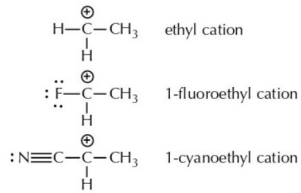


(a) Provide a drawing of the transition state structure for the mechanism step **G** -> **I-1**. Use dotted lines for partial bonds and indicate partial charges.

(b) Provide the curved arrow mechanism for the mechanistic step **I-1**-> **I-2**. Show both **I-1** and **I-2**.

(c) Provide a brief sentence that explains the origin of the regioselectivity of this reaction.

4.21 A study of carbocations has shown that the 1-fluoroethyl cation is 10.3 kcal/mol more stable than the ethyl cation, whereas the 1-cyanoethyl cation is 18.4 kcal/mol less stable than the ethyl cation. Use words and structural drawings to explain these observations.



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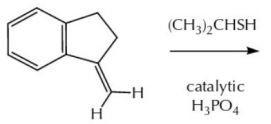
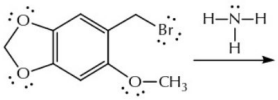
4.22 Each of the following reactions falls into one of the four fundamental classifications. Based on the information presented in each case, first identify the proper classification, and then apply that concept to complete the balanced chemical equation. In the case of addition reactions that can produce regioisomers, give the major product.

(a)



classification:

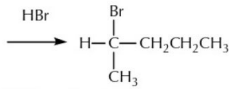
(b)



classification:

(c)

classification:

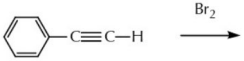


highly regioselective reaction

(d)

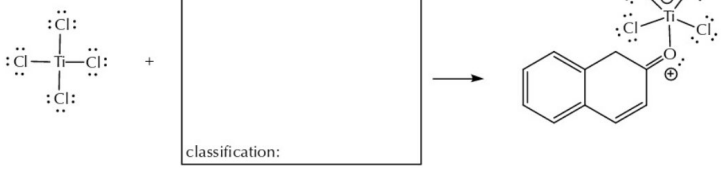
classification:

(e)



classification:

(f)



classification:

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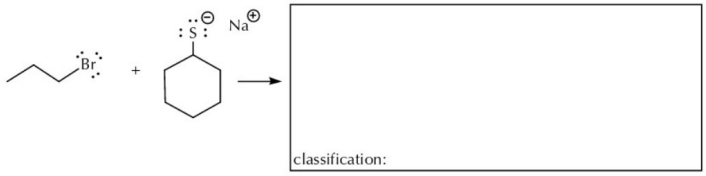
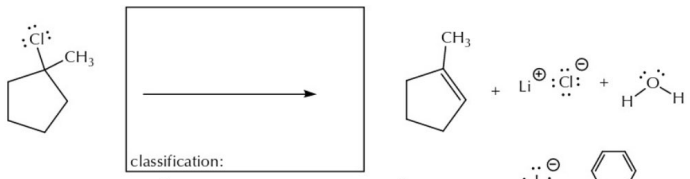
4.23 Each of the following reactions falls into one of the four fundamental classifications. Based on the information presented in each case, first identify the proper classification, and then apply that concept to complete the balanced chemical equation. In the case of addition reactions that can produce regioisomers, give the major product.

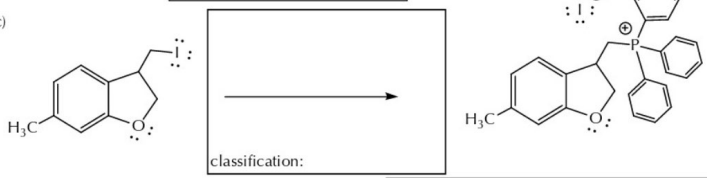
(a)



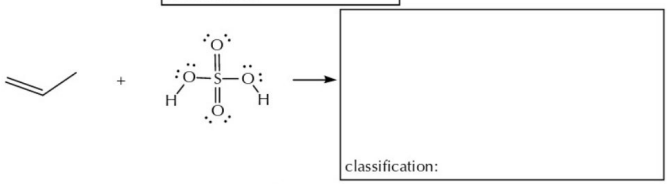
(b)



(c)



(d)



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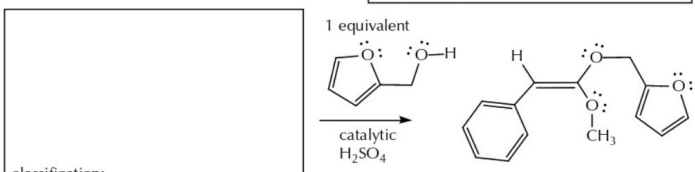

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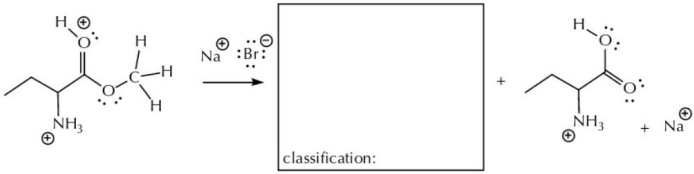

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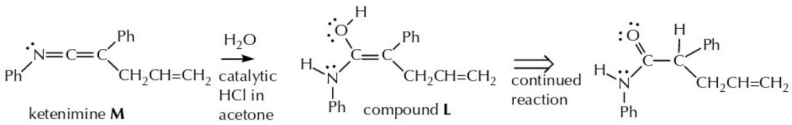
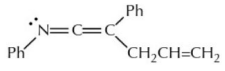
4.24 The mechanism for the addition of water to ketenimines (e.g., ketenimine **M**, below) using a strong acid catalyst takes place with all closed shell atom intermediates (*Org Lett*, **2017**, *19*, 5822).



ketenimine **M**

(a) Provide the intermediates and curved arrow mechanism for the steps, as described or outlined below.

protonation of ketenimine by the most likely acid in solution gives intermediate K_1



ketenimine **M**

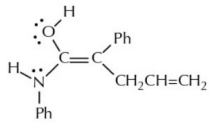
reaction between intermediate K_1 and water to give intermediate K_2

intermediate $\mathbf{M_1}$

reaction between intermediate K_2 and another equivalent of water to give compound L

intermediate $\mathbf{M_2}$

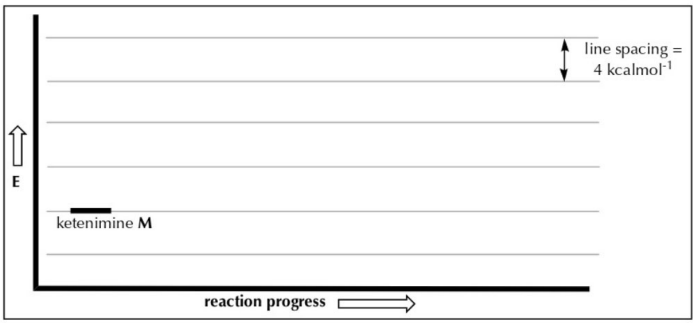
and



compound **L**

(b) Given these data, draw the Energy Diagram for the reaction:
ketenimine **M** to $\mathbf{M_1}$ $\Delta G^\circ = +12$ kcalmol^{-1}
intermediate $\mathbf{M_1}$ to $\mathbf{M_2}$ (rate-determing step) $\Delta G^\circ = -8$ kcalmol^{-1}
intermediate $\mathbf{M_2}$ to **L** $\Delta G^\circ = -8$ kcalmol^{-1}

Precise values on the graph for the transition state levels are not required, but you must show curves that are consistent with information given about the rate-determining step.



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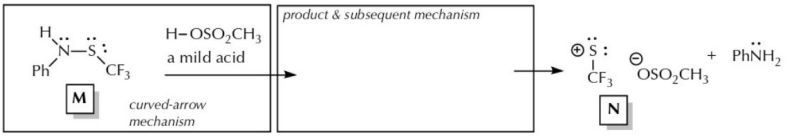
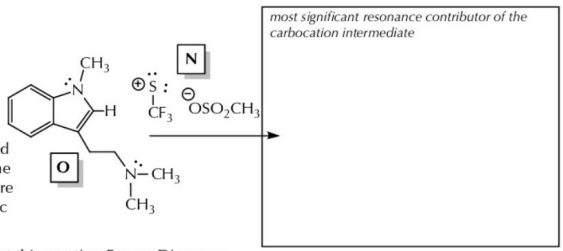
4.25 When compound **M** is treated with a mild acid, a reactive intermediate (**N**) is formed (*J Org Chem*, **2012**, *77*, 7538).

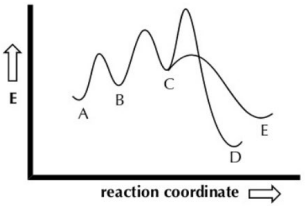
(a) Provide three things:
(i) the curved arrow mechanism for the Bronsted acid-base reaction between **M** and the mild acid,
(ii) the structure of the product, and
(iii) the curved arrow mechanism for the formation of **N**.



(b) This reactive intermediate (**N**) behaves as a strong electrophile (like a proton) for a variety of electrophilic addition reactions. Provide the most significant resonance contributor for the anticipated carbocation intermediate when **N** is combined with compound **O**. Reminder: The double bonds in benzene rings are less reactive towards electrophilic addition than others.



4.26 Answer the following questions about this reaction Energy Diagram:



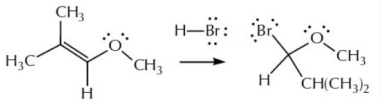
(a) rate determining step for A -> E? to

(b) major product if all steps are irreversible?

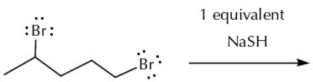
(c) major product if all steps are reversible?

(d) step with smallest energy of activation? to

4.27 When HBr adds to the double bond in methyl vinyl ketone, a product forms with high regioselectivity. Use words and drawings to explain this observed regioselectivity.



4.28 There are two sp^3 C-Br bonds in the following compound. The rate of the substitution reaction, using 1 equivalent of sodium sulfide (NaSH), is 40–50 times faster with the primary bromide than with the secondary bromide. What is the structure of the product, based on this fact, and what is the explanation for the observed selectivity?



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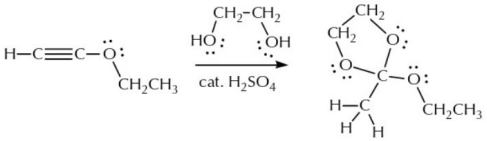
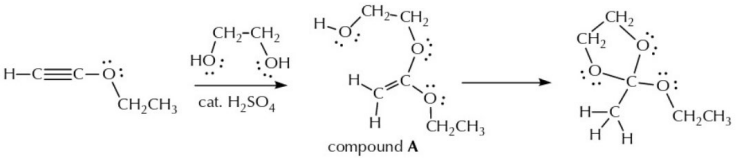
4.29 The electrophilic addition reaction shown on the right is observed. As you can see in the structure of the product, both of the pi bonds in the triple bond of the starting material are added to by the alcohol groups in the weak acid reagent, $HOCH_2CH_2OH$.



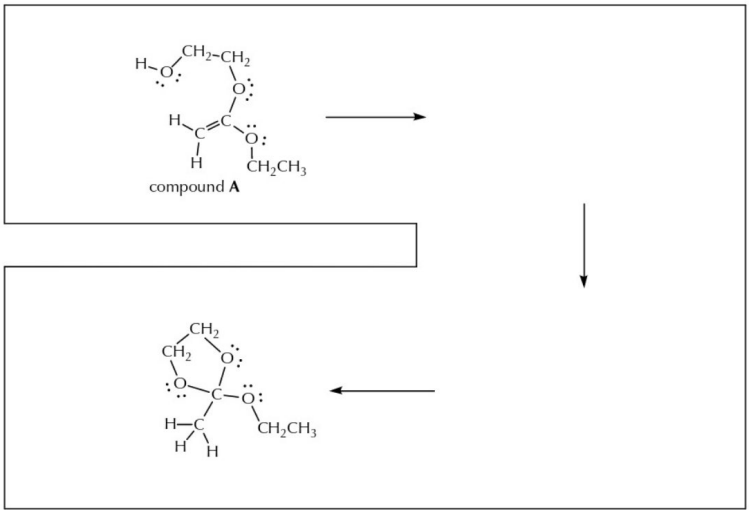
(a) What is the structure of the Brønsted acid in highest concentration in this solution (i.e., most available for carrying out reactions)?

(b) There are two addition reactions that take place here. The first addition reaction produces compound **A**, which undergoes an intramolecular (within the same molecule) addition to give the observed product.



compound **A**

Provide the complete, stepwise mechanism for the reaction, starting from compound **A** and ending with the observed product. You should use the most available Brønsted acid (from part a, above) as your Brønsted acid, and its conjugate base as a Brønsted base, when you need one. Although this is an intramolecular reaction, all three of the steps are exactly in analogy with any one of the intermolecular reactions you have seen.



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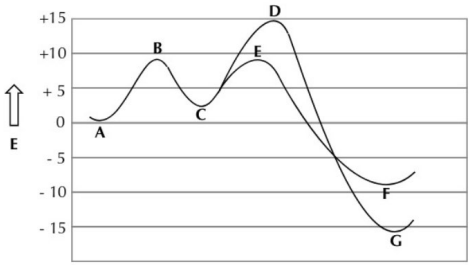
4.30 Compound **A** reacts to give two products **F** and **G**. The energy diagram for a particular example of a chemical reaction meeting these criteria derives from a published source (*J Org Chem*, **2000**, *65*, 6601).



Energy relative to A
B + 9.3 kcal/mol
C + 3.0
D + 15.0
E + 8.9
F - 13.2
G - 16.6

Answer the following questions concerning this energy diagram that describes the conversion of starting material **A** to products **F** and **G**. Place the letter or letters corresponding to the answer(s) in the answer spaces.

(a) Which point(s) on the diagram corresponds to transition state(s)?

(b) What is the rate-determining step for the transformation of **A** to **G**?

(c) If the formation of **F** and **G** are reversible (thermodynamic control), which product will dominate at equilibrium?

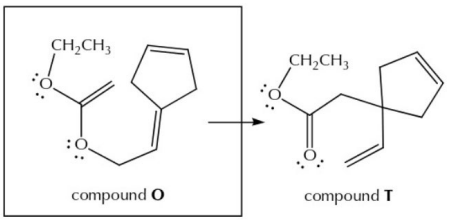
(d) What is the value of the activation energy for the **C** to **F** step?

(e) What is the value of the ΔG° for the formation of the most stable product?

(f) If the formation of **F** and **G** are irreversible (kinetic control), which product will dominate?

4.31 When compound **O** is heated, it undergoes the isomerization shown here, to form compound **T** in one smooth step that does not involve an intermediate (based on *J Org Chem*, **2005**, *70*, 7028).

(a) Provide the curved arrow mechanism that accounts for this isomerization.



compound **O** compound **T**

(b) Provide a drawing for the transition state structure; use dashed lines for partial bonds indicate any partial charges.

4.32 Compound **X** is one of the $C_5H_{11}Br$ structural isomers. It contains a tertiary bromide. It can be prepared from compound **W**, which contains a trisubstituted double bond, in a highly regioselective addition reaction of HBr. Based on this information, what are the structures of compounds **X** and **W**?

compound **W** HBr compound **X**

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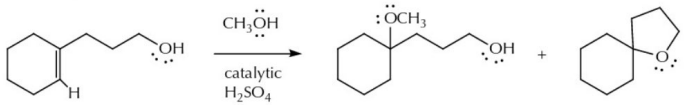
4.33 When compound **D** is treated with methanol (CH_3OH) and a catalytic amount of sulfuric acid (H_2SO_4), a mixture of two different products, compounds **E** and **F**, are observed.



compound **D** compound **E** compound **F**

Compound **D** undergoes a reaction with the conjugate acid of methanol to give intermediate $\mathbf{D_1}$.

Intermediate $\mathbf{D_1}$ has two fates:

(1) some of $\mathbf{D_1}$ goes on, in 2 steps, to give compound **E**
(2) some of $\mathbf{D_1}$ gives intermediate $\mathbf{D_2}$, which, after one more step, gives compound **F**

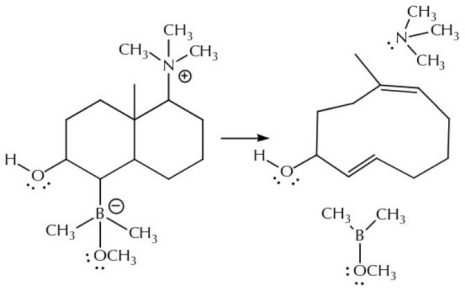
Provide (a) the structure of intermediate $\mathbf{D_1}$, (b) the curved-arrow mechanism for the formation of, as well as the structure for, intermediate $\mathbf{D_2}$.

intermediate $\mathbf{D_1}$
& the curved arrow mechanism for getting to $\mathbf{D_2}$

structure of intermediate $\mathbf{D_2}$

D → → F

4.34 The following transformation is known to occur in one mechanistic step. Draw a representation for the anticipated transition state structure using dotted lines for partial bonds, and including any required partial charges.



4.35 There are two $C_6H_{14}O$ isomers (compounds **G** & **H**) that contain a primary alcohol and a quaternary carbon atom. One of them (compound **H**) can undergo an elimination reaction of water, while the other (compound **G**) cannot. Based on this information, draw the structures for compounds **G** and **H**, as well as the structure of the dehydration (elimination of water) product from compound **H**.

compound **G** | compound **H** → dehydration of compound **H**

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4.36 The following pentavalent phosphorous compound is observed to give the following reaction.

Based on research studies, the reaction mechanism is proposed to occur in two steps.

Step 1: an addition reaction between the C=O and P=C, through a 4-membered ring transition state with no partial charges, to give a 4-membered ring intermediate

Step 2: a reversal of that reaction, through a second 4-membered ring transition state with no partial charges, to give the observed products

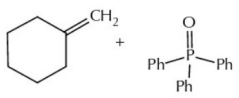
(a) Draw: (i) the curved arrow mechanism between the two starting materials (Step 1)
(ii) the transition state structure for Step 1
(iii) the 4-membered ring intermediate
(iv) the curved arrow mechanism for Step 2
(v) the transition state structure for Step 2

(i) the curved arrow mechanism between the two starting materials (Step 1)

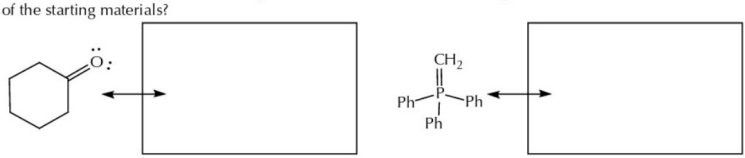
(ii) the transition state structure for Step 1

(iii) the 4-membered ring intermediate
(iv) the curved arrow mechanism for Step 2

(v) the transition state structure for Step 2



(b) The next most significant resonance contributors for both starting materials are used to explain the orientation between these two reactive partners as they collide. What are the next most significant resonance contributors for both of the starting materials?



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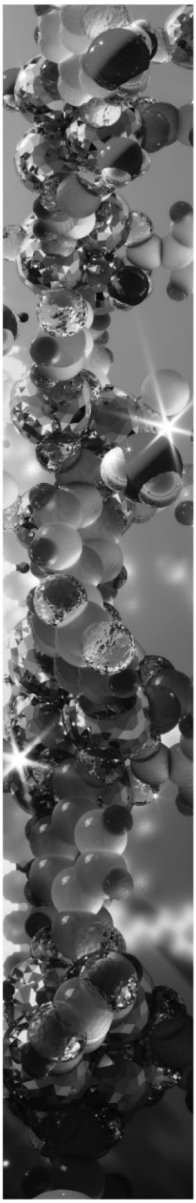

CHAPTER 5

Stereoisomerism of Organic Molecules

Setting the Stage: Not Everyone Believed It

5.1 Structural Isomerism: Naming Organic Compounds and the Detection of Molecular Symmetry

- A. What's in a Name?
- B. Organic Chemistry Nomenclature: Alkanes, Cycloalkanes, Alkenes, Alkynes, Alcohols, and Alkyl Halides
- C. Molecular Symmetry: Equivalent Sets of Atoms
- D. Detecting Molecular Symmetry: Introduction to Nuclear Magnetic Resonance (NMR) Spectroscopy

PRACTICE QUESTIONS

5.2 Sources of Stereoisomerism

- A. Stereoisomerism
- B. Double Bonds That Are Unsymmetrically Substituted at Both Ends
- C. Symmetrical Rings with an Even Number of Atoms and Substituted at Opposite Vertices
- D. Tetrahedral Atoms with Four Different Substituents

PRACTICE QUESTIONS

5.3 Chirality and Optical Activity in Molecules with a Single Source of Stereoisomerism

- A. Detecting and Defining Handedness in the Macroscopic and Nanoscopic Worlds
- B. Tetrahedral Atoms with Four Different Substituents
- C. Double Bonds That Are Unsymmetrically Substituted at Both Ends
- D. Symmetrical Rings with an Even Number of Atoms and Substituted at Opposite Vertices

PRACTICE QUESTIONS

5.4 Chirality and Optical Activity in Molecules with Multiple Sources of Stereoisomerism

- A. Molecules with More Than One Chiral Stereocenter (Unsymmetrical, Dissimilar Centers)
- B. Molecules with More Than One Chiral Stereocenter (Symmetrical, Similar Centers)
- C. Other Molecules with Multiple Sources of Stereoisomerism
- D. From Molecular Formula to Structural Isomers to Stereoisomers

PRACTICE QUESTIONS

Reflections About Science: The Same and Not the Same

Summary

CHAPTER QUESTIONS

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CHAPTER 5

Stereoisomerism of Organic Molecules

Setting the Stage: Not Everyone Believed It

The scientific history of how chemists began thinking about molecular structures in three dimensions (stereochemistry) is an exemplar lesson in how new ideas are sometimes resisted, and in the different roles for scientific skepticism in how ideas evolve.

In Chapter 1, a rather provocative idea is presented, that humans invented (rather than "discovered") organic molecules. I intentionally used the verb "invented" because there was no direct evidence for molecules. Instead, the concept of molecular structure was a hypothesis that solved a problem. In particular, the problem of different substances with the same elemental composition was solved with a leap of logic, namely, by imagining the organized connectivity of atoms as molecular structure, decades before any direct experimental evidence for connectivity existed. And not everyone believed it, which is as typical in science as it is in any other human endeavor.

Progress in science is always accompanied by debates, controversies, and skepticism. At the edge of our understanding of anything, in the absence of facts, there are competing hypotheses for why things happen. The competing hypotheses represent different explanations, and these explanations result in different predictions. Experiments are designed to test predictions; they provide evidence and can disprove the hypotheses that are inconsistent with the experimental results. Scientific skepticism is sometimes misunderstood as simply being recalcitrant, of stubbornly sticking to your idea because you want it to be true. A more productive view of scientific skepticism is not buying into the first story (hypothesis) you hear, and instead being able to construct as many different hypotheses as possible that can coherently account for all of the data and observations without needing to invoke unusual and/or supernatural forces.

Sometimes there are wild ideas proposed in science, so far outside the human experience that it is impossible to tell if they are insightful and revolutionary or simply far-fetched fantasies. To sort these options out, skepticism takes on another form: the demand for evidence. The more unprecedented and unusual a claim is, the greater the demand for evidence which supports that claim and not the many other possible explanations.

What are the real versus imagined limits on human achievement and understanding? History is replete with examples of one version or another of the belief that "it ain't gonna fly, Orville" (a reference to the Wright Brothers and lighter-than-air flight) and perceived limits (breaking the sound barrier, running a 4-minute mile). And without direct evidence, scientists are rightfully skeptical, no matter how attractive an idea is or how much we would like something to be true. Holding back on what will end up being the good ideas means that we are also holding back on the bad ideas, too, and so skepticism can also prevent harmful things from getting out of hand.

Evidence and information alone are not enough, either in scientific thought or in human behavior. We have more than enough evidence, for example, that smoking tobacco, consuming too much sugar, and being too sedentary create negative effects on long-term health, but changing behaviors and beliefs is not a matter of instant enlightenment. The same is true in science, where there can be an all-too-human

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desire for the familiar. Recall the anxiety expressed by Liebig (Chapter 2), on how strongly people want to hold on to their ideas: *the most beautiful theories are destroyed by these damned experiments*. And more severely by Planck (Chapter 1): *old ideas finally die when those who hold them die*. People resist change, in general, and want to uphold the status quo. In modern medicine, there was great resistance to the idea that nitric oxide (NO), which is toxic at levels of 100 ppm in air, is also a natural signaling molecule in mammals, including humans, and the concept was severely criticized. In another dramatic example from the 1980s, a scientist who had strong evidence that many diagnosed stomach ulcers were caused by *H. pylori* bacterial infections, rather than eating spicy foods or psychological stress, deliberately infected himself and demonstrated the efficacy of antibiotics as a treatment.

Moving now into the topic of stereochemistry, the study of how the three-dimensional structure of molecules affects their properties. As implied by the title of this chapter, stereoisomerism refers to isomerism (different molecules) in which molecules have the same connectivity, but differ because of the three-dimensional arrangements of their atoms in space ("stereo-" as in stereoscopic vision, refers to three-dimensionality and its perception).

Recall my statement, above, that humans invented molecules (connectivity) in the early 1800s to solve a problem: Substances with the same elemental composition demonstrated different properties. Until then, elemental composition is what was thought to give substances their uniqueness. Quite comparably, about 50 years later, the proposal for the three-dimensional arrangement of atoms solved another isomerism problem: There are molecules with the *same connectivity* that demonstrated different properties. Connectivity of atoms in a molecular structure was not enough to explain these observations, and three-dimensional arrangements of atoms was the revolutionary hypothesis. And although direct experimental evidence for the three-dimensional structures of the most relevant organic molecules would not be obtained for nearly a century, the hypothesis for the tetrahedral shape of atoms solved some long-standing problems about understanding molecular structure.

The story of stereochemistry begins with mineralogy. For a long time, people knew that the naturally occurring mineral, quartz, had two different crystalline forms, and that they were related to one another as nonidentical mirror images, as does any object referred to as having a right- and left-handed partner (shoes, gloves, scissors, spirals). Quartz crystals are said to be either the right-handed version or the left-handed version. Until 1811, these two different crystal forms were observed to have identical properties. In that year, however, using a special form of light (called plane-polarized), the right- and left-handed quartz crystals were observed to have equal yet opposite effects on this light, a property that was called optical activity.

Over the next 30 years, apparently identical organic molecules (same connectivity) were also observed to have different optical activities. Sometimes they were inactive, sometimes they showed the same equal and opposite character as the quartz crystals. What was particularly puzzling is that these observations were not on solid phase materials with obvious crystalline structures, but on gas and solution phase samples. In 1874, two scientists (Joseph Le Bel, a chemist from France, and Jacobus van't Hoff, a Dutch chemist who was employed at a veterinary school) simultaneously proposed the idea that the three-dimensional molecular architecture of tetrahedral atoms could be used to explain the differences in properties observed in these molecules.

And as before, not everyone believed the revolutionary idea that the three-dimensional arrangement of atoms was needed as an explanation. One can only imagine that the following stinging criticism leveled at the 22-year old van't Hoff, written by one of the renowned chemists of the day, Hermann Kolbe, then 56, might appear today on some social media outlet. Kolbe was the editor of the *Journal für praktische*

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Chemie and frequently used this platform to make his points. He wrote a two-part editorial ("Ziechen der Zeit" – A Sign of the Times) in 1876 and 1877.

> "One of the reasons for the contemporary decline of chemical research in Germany [is] the lack of well-rounded as well as thorough chemical education. Many of our chemistry professors labor with this problem to the great disadvantage of our science. As a consequence of this, there is an overgrowth of the weed of the seemingly learned and ingenious but is in reality trivial and stupefying natural philosophy. This natural philosophy, which had been put aside by exact science, is at present being dragged out by pseudoscientists from the junk-room which harbors such failings of the human mind and is dressed up in modern fashion and rouged freshly like a whore whom one tries to smuggle into good society where she does not belong."
>
> "A Dr. J. H. van't Hoff of the Veterinary School at Utrecht has no liking, apparently, for exact chemical investigation. He has considered it more convenient to mount Pegasus (apparently borrowed from the Veterinary School) and to proclaim in his '*La chimie dans l'espace*' how, in his bold flight to the top of the chemical Parnassus, the atoms appeared to him to be arranged in cosmic space. I should have taken no notice of this matter had not Wislicenus [another renowned senior organic chemist] oddly enough written a preface to the pamphlet, and not by way of a joke but in all seriousness recommended it a worthwhile performance."
>
> H Kolbe, *Journal für praktische Chemie* Band *123*, **1877** (**15**, 473 ff.)

One other historical footnote: 27 years later, Jacobus van't Hoff received the first Nobel Prize in Chemistry, in 1901, for his contributions to theoretical chemistry.

Stereochemistry, the study of stereoisomers and their properties, is a well-established area of chemistry and an essential feature in biochemistry and pharmaceutical sciences. Even more strongly than when three-dimensional structures were introduced earlier in the text, I urge you to get—*and use!*—a physical set of molecular models, so that you can properly understand the relationship between the two-dimensional drawings we use to represent three-dimensional objects and the objects themselves. If you use computer-based models, be sure you are using stereoscopic information (systems that require special glasses), that is, a system that provides each of your eyes with different input, which is how your brain perceives the three-dimensional world.

5.1 Structural Isomerism: Naming Organic Compounds and the Detection of Molecular Symmetry

A. What's in a Name?

Throughout history, humans have used, and continue to use, a variety of systems to name chemical substances. Observable properties are perhaps the most obvious method. The word "gold" derives from the same root as "gilded," meaning shiny and yellow, reflecting (or capturing) the properties of the sun. And the word "acid" refers to a specific taste, while the compound named "putrescine" is definitely not one you would like to smell. The painkiller morphine was named for Morpheus, the Greek god of dreams. The practice continues to this day. When the body's naturally occurring cannabinoid (interacts with the same receptor site as the psychoactive tetrahydrocannabinol, THC, compounds found in marijuana) was discovered in 1992, its discoverers named it "anandamide," which is derived from the Sanskrit work for bliss.

Locations have also been a popular source of names. The word "ammonia," and then "amine," derives from the Temple of Ammon, where deposits of ammonium chloride (the salt of Ammon) were common

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as a decomposition product of animal dung. Cadaverine, closely structurally related to putrescine, occurs in decaying animal tissues.

As chemistry matured, the nomenclature became more chemically oriented. The words "hydrogen" (water-bringer) and "oxygen" (acid-bringer) were created to reflect chemical properties. The molecular classification name "aldehyde," of which the example of formaldehyde is likely to be familiar, is a contraction of the original term "alcohol dehydrogenatus." The structural relationship between an alcohol and an aldehyde is dehydrogenation (loss of hydrogen, an elimination reaction, from an alcohol).

By the end of the nineteenth century, the number of organic compounds that were being synthesized or isolated from natural sources was growing rapidly. Under these conditions, it eventually became impossible for chemists to learn the names randomly assigned to compounds by their discoverers, especially when the names showed no correlation to the molecular structures.

Since 1892, chemists from all over the world have met periodically to decide on systematic rules for naming organic compounds. These rules, which are constantly evolving, are called the *International Union of Pure and Applied Chemistry* (abbreviated as IUPAC) rules. The IUPAC system of nomenclature was developed so that each organic compound would have a unique name that would allow the structural formula to be written from it.

Ideally, a chemist would have to learn only the systematic names of compounds. In the real world, however, there are three complications. First, even the IUPAC rules allow for some variations in the naming of compounds. Second, the correct IUPAC names for some compounds are so complicated and cumbersome that everybody continues to use the common, unsystematic names for them. As illustrated above, the names derive from the natural origins of compounds, reactivity or physical properties, or sometimes even the whimsy of their creators.

Finally, and perhaps most importantly, many compounds had names before the IUPAC rules came into being, and these names are still used, especially by chemical supply houses, by industry, and they appear on the hundreds of thousands of pages of journal articles and books from the last 200 years that will never be edited to update names. To be literate in the laboratory, you must be able to recognize many common names. Therefore, while the emphasis in this book is on the systematic names of compounds, the common names of important compounds are also given and are used in cases where they are the ones used overwhelmingly by chemists in their daily work.

B. Organic Chemistry Nomenclature: Alkanes, Cycloalkanes, Alkenes, Alkynes, Alcohols, and Alkyl Halides

Every decade or so, the IUPAC needs to update its organic nomenclature rules (called the "Blue Book," first published in 1979) to account for new discoveries. In this text, you will be responsible for learning barely a few pages of the *Blue Book*, which contains the rules for naming millions of compounds.

As you learn to name organic molecules, you will soon begin to think of cases that are not covered by the rules you have learned. Rest assured that the rules exist. For now, stay within the boundaries of the molecules that you are responsible for. The first batch of organic molecules you are formally responsible for naming are alkanes, cycloalkanes, alkenes, alkynes, alcohols, and alkyl halides.

The IUPAC rules are quite systematic, and the process of learning how to name organic molecules is useful because it gives you excellent practice in analyzing molecular structures. Appendices 2 and 4 (Book B) contain the basic rules, and some exercises, for naming these six classes of organic molecules. Figure 0501 contains a collection of molecular structures (and their names) that are representative of the structures you should be able to name after completing Appendices 2 and 4 (Book B).

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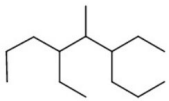
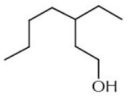
Figure 0501

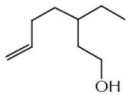
Representative structures and their names based on the guidelines in Appendix 2.



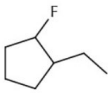
4,6-diethyl-5-methylnonane



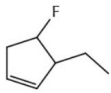
3-ethylheptan-1-ol



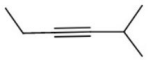
3-ethylhept-6-en-1-ol



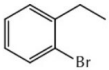
1-ethyl-2-fluorocyclopentane



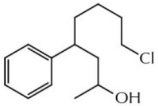
3-ethyl-4-fluorocyclopent-1-ene



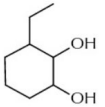
2-methylhex-3-yne



1-bromo-2-ethylbenzene



8-chloro-4-phenyloctan-2-ol



3-ethylcyclohexane-1,2-diol

C. Molecular Symmetry: Equivalent Sets of Atoms

In Chapter 4, you learned that the electrophilic addition reaction of strong and weak Brønsted acids to pi bonds can give highly regioselective reactions. Although the results from many years of experiments were provided, none of the actual experimental evidence was given, particularly how chemists go about determining molecular structures.

Starting in this section, the results from various experimental methods will be included as evidence for how conclusions are drawn about organic molecular structure. Details about experimental procedure are best left to a laboratory course, where you can get the firsthand experience.

Typical laboratory information includes the molecular formula, which immediately gives a bit of structural information (units of unsaturation), and physical properties such as boiling point, melting point, which help establish that two substances are different and, when they are sharply defined values, indicate homogeneity (purity) of the sample. The relative magnitudes of molecular dipole moments can reveal features of molecular geometry when isomers are compared.

Fast and convenient experimental measurements that reveal information about the connectivity of a hydrocarbon structure have been commercially available since the late 1950s. As you might predict, getting direct information about molecular connectivity meant that structures could be assigned to compounds rapidly and reliably, and the better the structural information, the better the evidence, and the easier it was to test hypotheses and predictions about reaction outcomes. The experimental method, called nuclear magnetic resonance (NMR) spectroscopy, revolutionized the practice of experimental organic chemistry in the 20th century. While research-grade NMR instruments can cost millions of dollars, there are also benchtop instruments that can be used in undergraduate teaching labs that are a fraction of the cost and can provide immediate and useful information for beginning students to test out their own ideas.

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Understanding the data that NMR spectroscopy produces requires an introduction to how to think about how the symmetry of molecular structures can produce equivalent groups of atoms. We will use methane (CH_4), ethane (CH_3CH_3), and propane ($CH_3CH_2CH_3$) as the first examples to illustrate what is meant by groups of equivalent atoms in a structure.

In methane (CH_4), there is one carbon atom. All four hydrogen atoms are equivalent to one another, comprising one set of four hydrogen atoms, sitting at the corners of a tetrahedron. If you could occupy one of the four spots, it would be strictly identical to the other three. Methane has one carbon atom and one group of four equivalent hydrogen atoms.

In ethane (CH_3CH_3), there are two carbons, but they are equivalent to one another, each bearing three hydrogen atoms and indistinguishable from each other. There is one set of equivalent carbon atoms in ethane. All six of the hydrogen atoms are equivalent: No matter which hydrogen atom you are, you are indistinguishable from the other five because of the symmetry of the molecular structure. Ethane has one group of two equivalent carbon atoms and one group of six equivalent hydrogen atoms.

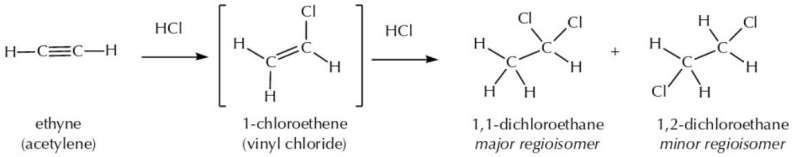
In propane ($CH_3CH_2CH_3$), the two carbons at the end of the chain are identical, but different from (nonequivalent to) the one in the center. The group of six hydrogen atoms on those two end carbons are equivalent to one another, while they are different from the two hydrogens on the center carbon atom. Propane has two groups of equivalent carbon atoms (a group of two and a group of one) and two groups of equivalent hydrogen atoms (a group of six and a group of two).

As you will see, later, NMR spectroscopy can provide information about the number and relative sizes of groups of carbon and hydrogen atoms in a structure. Before showing that experimental data, however, we will first go a little deeper into how to think about molecular structures in terms of overall molecular symmetry that produces groups of equivalent atoms.

Figure 0502 illustrates an electrophilic addition reaction. Starting with ethyne (acetylene), the addition of excess hydrochloric acid (HCl) first gives 1-chloroethene (vinyl chloride) and then, upon addition of a second equivalent of HCl, a mixture of regioisomeric products, 1,1-dichloroethane and 1,2-dichloroethane. According to Markovnikov's Rule, the 1,1-dichloroethane is predicted to be the major regioisomer (and it is). An accurate determination of the structures is critical to understanding this or any other reaction, and in this part of the chapter, you will begin to see how we determine which structure is which.

Figure 0502

The electrophilic addition reaction between ethyne and excess hydrochloric acid.



Both of these regioisomers have the same molecular formula, $C_2H_4Cl_2$, and while that information will affirm that these molecules have this molecular formula, it cannot tell you which one is which. Their physical properties are different, but without Markovnikov's Rule, you would not know which drawing represents the predicted major product and which is the minor. In the laboratory, you might determine that one of them has a boiling point of 83 °C, a melting point of -35 °C, and a molecular dipole moment of 1.42 Debye. And the other has a boiling point of 57 °C, a melting point of -97 °C, and a molecular

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dipole moment of 1.95 Debye. This information tells you that the two compounds are different structural isomers (same formula, different properties), but it would not tell you which one is which. And arriving at Markovnikov's Rule, or any conclusion about the reaction whatsoever, requires that you can identify the molecular structures hidden in what appear, to you, to be two clear, colorless liquids with pungent odors.

Prior to the late 1950s, the most useful identification method was to compare the properties of an unknown material to the libraries of known compounds, hoping that the data would line up and you could make a positive comparison. If a positive comparison could not be made, the unknown was subjected to chemical procedures that would either transform it into something new, and then those properties could be compared, or one would literally break the unknown into smaller molecular pieces (decompose it, carefully) with the hope that those pieces could be identified and then reconstructed into the identity of the original unknown. This process was rather like having an unknown mechanism locked inside of a box, and if you could not figure out what that object was, you had it taken apart and tried to reconstruct it from the pieces (as long as you recognized the pieces). For complex organic structures, this process might take years. And ultimately, the identification relied on preparing the suspected structure independently (organic synthesis) and comparing the properties of the synthetic compound with the original unknown.

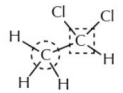
Throughout the first half of the twentieth century, experimental methods called spectroscopy were developed for more directly getting information about organic molecular structures. Different parts of the electromagnetic spectrum are absorbed in different ways by organic molecules, and information-rich correlations between these absorptions and molecular structure rapidly resulted. In the most generally useful of these methods, NMR spectroscopy, direct information about molecular symmetry can be obtained for the carbon and hydrogen atoms in an organic molecule.

Returning to the two $C_2H_4Cl_2$ regioisomers (Figure 0503): The molecular symmetries of their structures are quite different. Using the same method as in the methane/ethane/propane comparison, above, we can establish the relative number and sizes of the equivalent groups of carbon and hydrogen atoms in these two molecular structures.

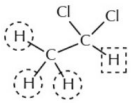
Figure 0503

Analysis of molecular symmetry in the dichloroethane regioisomers.

1,1-dichloroethane

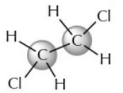


the two carbon atoms are different from each other (nonequivalent) because one of them is attached to 2 chlorine atoms and 1 hydrogen atom, while the other is attached to 3 hydrogen atoms
conclusion: 2 sets of carbon atoms

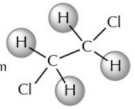


the four hydrogen atoms are two different (nonequivalent) groups because one of them is attached to carbon with 2 chlorine atoms, while the other three are attached to a lone carbon atom
conclusion: 2 sets of hydrogen atoms (3:1 ratio)

1,2-dichloroethane



the two carbon atoms are equivalent to each other because they are both attached to 1 chlorine atom and 2 hydrogen atoms
conclusion: 1 set of carbon atoms



the four hydrogen atoms are equivalent to one another because they are all attached to carbon atoms with 1 chlorine atom and 2 hydrogen atoms
conclusion: 1 set of hydrogen atoms

In 1,1-dichloroethane, the two carbon atoms are clearly distinctive (one of them has two chlorine atoms and one hydrogen atom attached, while the other carbon has three hydrogen atoms attached). Comparably, the four hydrogen atoms are not all equivalent. Three of them comprise one equivalent group (remember that the carbon is a tetrahedron, so all three of the hydrogen atoms are equivalently placed) while the one remaining hydrogen atom is unique. In 1,2-dichloroethane, the situation is quite different. The molecule is more symmetrical, and not only are the two carbon atoms equivalent to one another, all four of the hydrogen atoms are equivalently placed.

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Experimentally, getting this information about the structure is exceptionally useful because it differentiates them. In other words: If you were told that unknown regioisomer #1, the minor component in the reaction, had a molecular formula of $C_2H_4Cl_2$, that its two carbons were equivalent and that its four hydrogens were in a single equivalent group, you could conclude that its structure was 1,2-dichloroethane because that is the only connectivity that matches the experimental description. And if unknown regioisomer #2, the major component, was also $C_2H_4Cl_2$, had nonequivalent carbon atoms and its four hydrogen were in two groups with a 3:1 ratio, then you could piece that puzzle together and conclude that it was the 1,1-dichloroethane structure. One possible analytical sequence for these experimental data is shown in Figure 0504.

Figure 0504

Using experimental data to deduce the structures of the dichloroethane regioisomers.

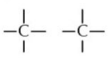
experimental data for unknown regioisomer #1

molecular formula: $C_2H_4Cl_2$

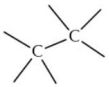
boiling point = 83 °C
melting point = -35 °C
dipole moment = 1.42 D

number of equivalent carbon atom groups = 1
number of equivalent hydrogen atoms groups = 1

step 1. the pieces:

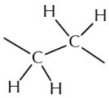


step 2. the carbons must be attached or more than one molecule results



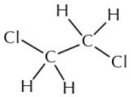
to be equivalent carbons, groups attached to both of them must be the same

step 3. four hydrogens can only be attached two ways: two on each carbon, or three on one and one on the other



to be four equivalent hydrogens, and maintain the two equivalent carbons, the only option is to have two hydrogens on each carbon

step 4. this leaves the two chlorine atoms and the other two equivalent, open bonding sites



conclusion: regioisomer #1 is 1,2-dichloroethane

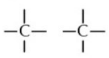
experimental data for unknown regioisomer #2

molecular formula: $C_2H_4Cl_2$

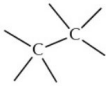
boiling point = 57 °C
melting point = -97 °C
dipole moment = 1.95 D

number of equivalent carbon atom groups = 2
number of equivalent hydrogen atoms groups = 2 (3:1 ratio)

step 1. the pieces:

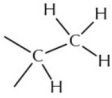


step 2. the carbons must be attached or more than one molecule results



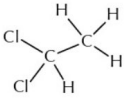
to be unequivalent carbons, groups attached to both of them must be the different

step 3. four hydrogens can only be attached two ways: two on each carbon, or three on one and one on the other



to be two sets of hydrogens in a 3:1 ratio, and maintain the two unequivalent carbons, the only option is to have three hydrogens on one carbon and one on the other

step 4. this leaves the two chlorine atoms to be bonded to the same carbon, maintaining the unequivalent groups of carbons and hydrogens



conclusion: regioisomer #2 is 1,1-dichloroethane

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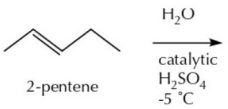
Start with the collection of atoms as separate pieces (step 1); these are the atomic building blocks. The two carbon atoms must be bonded to each other because all of the other atoms are monovalent. The analysis of the carbon atom symmetry (step 2) says that the two carbons in unknown #1 must end up with exactly the same groups attached to end up as equivalent, while in #2, the groups on each carbon need to be different. In step 3, the finite number of bonding sites afforded by carbon atoms is critical information because there are only 2 ways to divide up four hydrogen atoms between these two carbon atoms: either 2:2 or 1:3. To maintain the equivalence of the carbons and the hydrogens, unknown #1 must be 2:2, while the 1:3 ratio actually appears in the experimental information for unknown #2, so this is consistent. And finally (step 4) each structure has two open bond sites remaining and two monovalent chlorine atoms to attach.

Looking ahead, this type of experimental information is routinely available and rapidly obtained using NMR spectroscopy. As you can see, getting this type of information makes determining organic molecular structures significantly easier than it was prior to 1960, before the technique was available for routine use. Before looking at the actual experimental output from NMR spectroscopy, it is worth looking at a few more examples of the correlation between molecular symmetry, equivalent groups of atoms, and molecular structure.

Carried out at low temperature (-5°C), the electrophilic addition reaction of 2-pentene with water and catalytic sulfuric acid (a hydration reaction) gives a nearly 1:1 mixture of two different $C_5H_{12}O$ alcohols, compounds A and B (Figure 0505). The two molecular formulas are consistent with an addition reaction, and at this point you have a lot of precedent to think of that as a reasonable expectation. With a 1:1 mixture, there is no observed regioselectivity, and looking at the two ends of the double bond in 2-pentene, Markovnikov's Rule cannot be used to predict which of the two alcohols is the major outcome because the two ends of the double bond are equally substituted.

Figure 0505

Electrophilic addition of water to 2-pentene (hydration reaction), low temperature.



compound A + **compound B**

~ 1:1 ratio

experimental data for **compound A**

molecular formula: $C_5H_{12}O$

boiling point = 119 °C
melting point = -73 °C
dipole moment = 1.66 D

number of equivalent carbon atom groups = 5
number of equivalent hydrogen atoms groups = 6
ratio of hydrogen atoms is 1:1:2:2:3:3

experimental data for **compound B**

molecular formula: $C_5H_{12}O$

boiling point = 114-115 °C
melting point = -64 °C
dipole moment = 1.64 D

number of equivalent carbon atom groups = 3
number of equivalent hydrogen atoms groups = 4
ratio of hydrogen atoms is 1:1:4:6

Using prior chemical knowledge, the electrophilic addition reaction of water predicts two regioisomers:

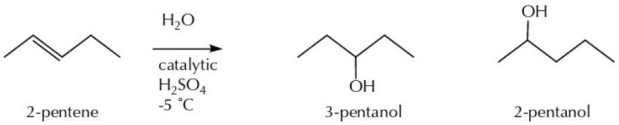


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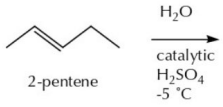
Figure 0506

Structural deduction of the low temperature hydration reaction products of 2-pentene.



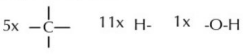
experimental data for compound A

molecular formula: a $C_5H_{12}O$ alcohol

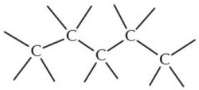
boiling point = 119 °C
melting point = -73 °C
dipole moment = 1.66 D

number of equivalent carbon atom groups = 5
number of equivalent hydrogen atoms groups = 6
ratio of hydrogen atoms is 1:1:2:2:3:3

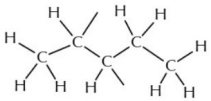
step 1. the pieces:



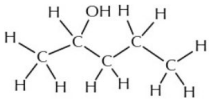
step 2. if we assume that the connectivity is maintained, then the five carbons remain bonded in a row



step 3. indeed, if the connectivity for all of the 2-pentene atoms is maintained, we know where 10 of the hydrogen atoms are



step 4. the experimental information says there are 6 sets of hydrogen atoms; attaching the remaining H onto the center carbon gives 5 sets [3:1:2:2:3] (while attaching to the other carbon creates molecular symmetry, resulting in 3 groups), and that leaves the hydroxyl group to attach, and unknown **A** is consistent with 2-pentanol



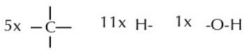
experimental data for compound b

molecular formula: a $C_5H_{12}O$ alcohol

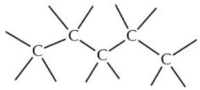
boiling point = 114-115 °C
melting point = -64 °C
dipole moment = 1.64 D

number of equivalent carbon atom groups = 3
number of equivalent hydrogen atoms groups = 4
ratio of hydrogen atoms is 1:1:4:6

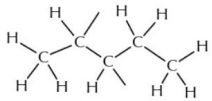
step 1. the pieces:



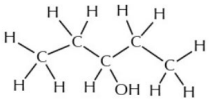
step 2. if we assume that the connectivity is maintained, then the five carbons remain bonded in a row



step 3. indeed, if the connectivity for all of the 2-pentene atoms is maintained, we know where 10 of the hydrogen atoms are



step 4. the experimental information says there are 4 sets of hydrogen atoms; attaching the remaining H onto the second carbon gives 3 sets [6:4:1], thanks to molecular symmetry (while attaching to the center carbon results in 5 groups), and that leaves the hydroxyl group to attach, and unknown **B** is consistent with 3-pentanol



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Using prior knowledge about organic reactions, you can predict that the electrophilic addition reaction should give a mixture of 3-pentanol and 2-pentanol. And it makes sense that the regioselectivity would be low because the two ends of the double bond are equally substituted. If the molecular descriptions match these predicted structures, then the experimental evidence would be consistent with these two compounds.

Compound A has an observed boiling of 119 °C, a melting point of -73 °C and a dipole moment of 1.66 Debye, while compound B has a narrow boiling range of 114–115 °C, a melting point of -64 °C, and a dipole moment of 1.64. These data tell you that the compounds are different but cannot be used to tell which one is which.

Experimentally (using the results from NMR spectroscopy), compound A is observed to have 5 sets of carbon atoms and 6 sets of hydrogen atoms (ratio 1:1:2:2:3:3), while compound B has 3 sets of carbon atoms and 4 sets of hydrogen atoms (ratio 1:1:4:6). Now we have some useful differences in molecular structure, but which one is which?

There is no prescribed method for solving one of these structural puzzles because so much depends on the information that is provided. Figure 0506 outlines a deduction pathway following the earlier (Figure 0504) model for the process.

One strategy might be to start with the two predicted structures, analyze them for their sets of equivalent groups, and then see if they match the reported data:

> The 3-pentanol structure is more symmetrical than 2-pentanol: With the hydroxyl group in the center of the 5-carbon chain, the 5 carbons are reduced to 3 sets, and the 12 hydrogens are reduced to 4 sets, in the ratio of 1:1:4:6. In the 2-pentanol structure, however, all of 5 of the carbons are different (any difference is a difference, and all of them are structurally situated differently), and only the hydrogen atoms co-located together on the same carbon atom are equivalent to one another, giving 6 sets of hydrogens in the ratio of 1:1:2:2:3:3. Note that it is not merely the distance from the oxygen atom that gives atoms their distinctive identities, but the entire molecular environment.

The analysis of the predicted structures matches the data. The analysis for 3-pentanol is consistent with the data for compound B; and analysis for 2-pentanol with compound A.

Sometimes, you have no predicted structures and/or the predictions do not match the data. A second strategy is the systematic analysis of the data to see if the molecular structures can be deduced, or at least narrowed down to a few options.

From these data, compound A is consistent with 2-pentanol and compound B is consistent with 3-pentanol.

Experimentally, you usually have an idea of the reaction outcome you are expecting. But quite often, chemical reactions do not proceed as advertised or a surprise shows up. Here is a nice example: In exactly the same hydration reaction of 2-pentene, as above, performing the reaction at a higher temperature (55°C instead of -5°C) is observed to give three $C_5H_{12}O$ alcohols, compounds A, B, and C. The experimental results are given in Figure 0507 on the next page.

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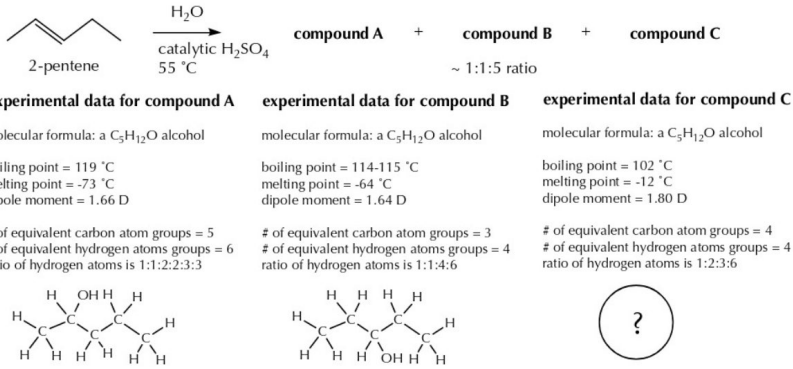
Figure 0507

High temperature electrophilic addition of water to 2-pentene (hydration reaction).


2-pentene
H_2O
catalytic H_2SO_4
55 °C
compound A + compound B + compound C
~ 1:1:5 ratio
experimental data for compound A
molecular formula: a $C_5H_{12}O$ alcohol
boiling point = 119 °C
melting point = -73 °C
dipole moment = 1.66 D
# of equivalent carbon atom groups = 5
# of equivalent hydrogen atoms groups = 6
ratio of hydrogen atoms is 1:1:2:2:3:3
experimental data for compound B
molecular formula: a $C_5H_{12}O$ alcohol
boiling point = 114-115 °C
melting point = -64 °C
dipole moment = 1.64 D
# of equivalent carbon atom groups = 3
# of equivalent hydrogen atoms groups = 4
ratio of hydrogen atoms is 1:1:4:6
experimental data for compound C
molecular formula: a $C_5H_{12}O$ alcohol
boiling point = 102 °C
melting point = -12 °C
dipole moment = 1.80 D
# of equivalent carbon atom groups = 4
# of equivalent hydrogen atoms groups = 4
ratio of hydrogen atoms is 1:2:3:6
?

What is happening here in the high temperature reaction? The only way to begin answering that question is to figure out what the three compounds are. Comparing the data with the earlier example, compounds A and B are exactly the same as in the low temperature reaction. But what is compound C, where did it come from, and why?

We can make the point strongly and clearly the first question *(What is compound C?)* is critical to answer before moving to the other questions *(Where did compound C come from? And why?)*. The situation of an unexpected product is an extremely common outcome in chemistry. The experimentally determined data are reported for compound C; we know

(a) compound C is an alcohol
(b) compound C has the molecular formula $C_5H_{12}O$
(c) compound C has different properties from compounds A and B, so these compounds are all structural isomers of each other
(d) compound C shows 4 sets of carbons and 4 sets of hydrogens (ratio 1:2:3:6).

As illustrated above, there is no single pathway for solving these puzzles, and practice will provide you with different strategies. We have no predicted outcome for a third isomer that is consistent with all past experience with addition reactions, so the method of starting with a predicted outcome is impossible. The deduction of the structure from the data, as is true in the laboratory, is the best available option.

Three important strategies to keep in mind while deducing a structure from the data are:

(1) comparing and cross-checking the different information for self-consistency as you make conclusions
(2) do not overinterpret the information too rapidly, and
(3) be prepared to reject any idea that is inconsistent across all of the data sources.

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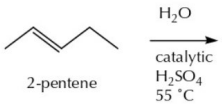
Your prior knowledge about organic molecules is also useful, such as, the well-behaved nature of the main group organic elements: You can bet that the carbons will have 4 bonds, the oxygen will have 2 bonds, and the hydrogens will each have 1 bond. Another useful fact is that the $C_5H_{12}O$ molecular formula has no units of unsaturation, and just like 2-pentanol and 3-pentanol, the unknown compound C can have no rings or multiple bonds in its structure.

A surprising but inescapable hypothesis is that the connectivity of the carbon atoms has changed. The 2-pentanol and 3-pentanol connectivities are already given, and the single other $C_5H_{12}O$ alcohol with all five carbons in a row is 1-pentanol. The 1-pentanol connectivity for compound C can be rejected as an option because it is inconsistent with the experimental data: 1-pentanol would have 5 groups of carbons and 6 groups of hydrogens in a 1:2:2:2:2:3 ratio. None of the three alcohols that maintain the five carbons in a straight chain is consistent with the data for compound C, and by following the data, we need to consider the possibility that the connectivity of the carbon atoms has changed. Do not be distracted by how this might take place. *As stated above: You need to figure out what the structure is before you can figure out how it might have been formed, not the other way around!*

Following the deductive scheme used in the prior examples, we start with all the pieces laid out (Figure 0508) and then begin to create clusters of atoms according to the number of groups and their relative sizes.

Figure 0508

Deducing the structure of the unknown product from the data in the high temperature hydration reaction of 2-pentene.



compound A 2-pentanol + **compound B** 3-pentanol + **compound C**

~ 1:1:5 ratio

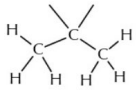
step 1. the pieces:

5x 11x H- 1x -O-H

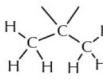
step 2. a set of 6 hydrogens can be 2x 3x 6x

is the only way to do it with this limited set of atoms; 3 CH_2 groups would need to be placed as a single eqivalent groups, as would 6 CH groups

2 equivalent CH_3 appear as a set of 6 in compound **B**, but that also required a set of 4 from the two equivalent CH_2 groups, and there are not those in compound **C**, so the two CH_3 groups are on the same carbon atom



step 3. from $C_5H_{12}O$, the set of 6 hydrogen atoms consumed 3 carbons, and the OH group is the set of 1 hydrogen (and the oxygen), which leaves 2 Cs and 5 Hs unaccounted for. With 4 total carbon atom groups, each of these remaining two must be nonequivalent, and there are two more hydrogen atoms groups [2:3 ratio], which means:

1x 1x to join with  and -O-H

step 4. and there is only one way to assemble these pieces (see step 5)

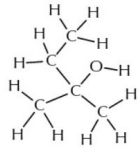
experimental data for compound C

molecular formula: a $C_5H_{12}O$ alcohol

boiling point = 102 °C
melting point = -12 °C
dipole moment = 1.80 D

# of equivalent carbon atom groups = 4
# of equivalent hydrogen atoms groups = 4
ratio of hydrogen atoms is 1:2:3:6

step 5. the proposed structure is consistent with the experimental data about the equivalent and nonequivalent sets of atoms



2-methyl-2-butanol

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The steps illustrated in Figure 0508 are expanded here. Reference the figure and sketch out what you might need to follow the logic in these five steps.

Step 1. Because the molecule is stated to be an alcohol, there is a hydroxyl group, and the oxygen atom must be attached to a carbon atom. This OH takes care of the group of "1" from the hydrogen atom sets, and it takes care of one of the carbon atoms as no other carbon can be like this one (there can only be one carbon attached to an oxygen), so that leaves 4 carbons to account for, along with 3 other sets of hydrogen atoms. *Structural conclusion:* The 1 hydrogen atom set is an OH group attached to a carbon [H-O-C].

Step 2. Understanding how to make a group of 6 hydrogen atoms is key to solving the structure, because (clearly!) all 6 hydrogen atoms cannot be attached to the same carbon atom. There are only three ways to get an equivalent set of 6 hydrogen atoms: (a) two groups of 3 hydrogens that are both equivalent to each other, (b) three groups of 2 hydrogens that are all equivalent to each other, or (c) six groups of 1 hydrogen that are all mutually equivalent. Of these options, only the two groups of 3 hydrogens are possible, because three groups of 2 hydrogens would consume 3 of the remaining 4 carbon atoms, not leaving enough behind to complete the structure.

Recall that compound B also had a group of 6 hydrogen atoms. There are two equivalently located CH_3 groups in 3-pentanol because of the overall molecular symmetry (there were also two equivalently located CH_2 groups). Compound C is not as symmetrical as compound B, so that means that the two CH_3 groups could be attached to the same carbon, which is the other way for them to be equivalent. *Structural conclusion:* The set of 6 equivalent hydrogen atoms is two equivalently located groups of 3 (CH_3 and CH_3) on the same carbon [$(CH_3)_2C$]

Step 3. Step 2 leaves only 2 carbons and 2 groups of hydrogen atoms with a 2:3 ratio unaccounted for. There is only one way to make this work. Structural conclusions: a CH_3 group that is different than the other two in Step 2, and a CH_2 group.

Step 4. There are 6 carbons proposed in these 4 clusters, so one of them is a duplication. In fact, with these 4 different clusters formed, there is only one way to assemble them into a rational structure: (a) the group of 6, the two equivalent CH_3 (methyl) groups, are attached to the carbon where the OH is located, as they need to be equivalent and leave at least one open valence for building the rest of the structure; (b) that leaves the CH2 group and the remaining CH_3 group to make an ethyl group which is, in turn, attached to the remaining bonding site at that carbon with the OH group.

Step 5. Go back and check for consistency with the overall experimental data. Compound C is a $C_5H_{12}O$ alcohol that shows 4 sets of carbons and 4 sets of hydrogens (ratio 1:2:3:6). This molecule (2-methyl-2-butanol) is consistent with these data.

The first question *(what is the structure of compound C?)* is answered. The second and third questions *(where did it come from and why?)* are topics for a later chapter. What matters here is an illustration about how information about the molecular symmetry can be used, along with other essential information, to deduce a molecular structure. A closer look at the actual experimental data is now presented in the next section.

D. Detecting Molecular Symmetry: Introduction to Nuclear Magnetic Resonance (NMR) Spectroscopy

The equivalence or nonequivalence of atoms or groups in a structure is observable experimentally, using nuclear magnetic resonance (NMR) spectroscopy. The details of NMR spectroscopy are discussed more fully in Appendix 9 (Book C) and the technique is typically a part in a laboratory course. In this introduc-

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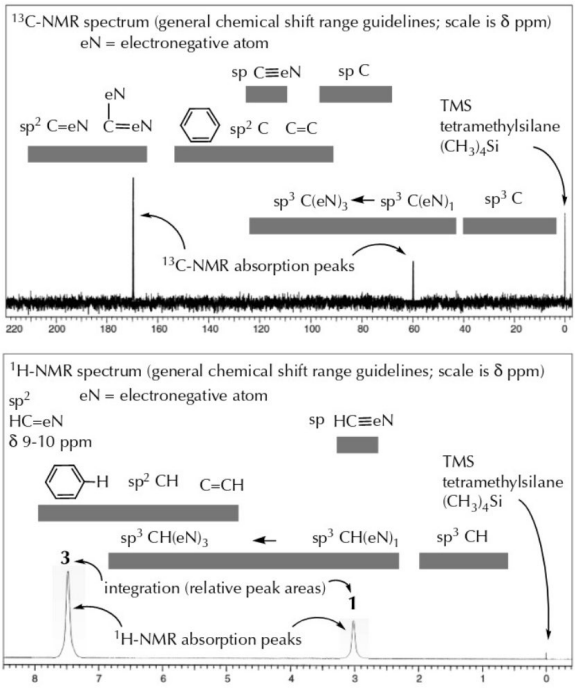
tion, we will focus on how NMR spectroscopy reveals the structural information featured in the previous section: the number of equivalent sets of carbon atoms in a structure, the number of equivalent sets of hydrogen atoms in a structure, and the ratio of the hydrogen atoms in those sets. Although it is possible to determine the ratio of carbon atoms in those sets, it is cumbersome and time-consuming to do, experimentally, and so it is not commonly performed.

The NMR experiment is sensitive to differences in isotopes. And so, ^{1}H-NMR spectroscopy is the commonly used hydrogen atom technique, and it is called "proton NMR," while ^{13}C-NMR spectroscopy ("C-13 NMR") is the commonly used technique for detecting carbons. Solvents for dissolving samples need to be free of ^{1}H-atoms or detecting the solvent would overwhelm the measurement, meaning that proton-free solvents are used (e.g., CCl_4 or solvents where the ^{1}H-atoms have been replaced by ^{2}H-atoms, such as deuterochloroform, $CDCl_3$, called chloroform-d, or hexadeuterobenzene, C_6D_6, called benzene-d6).

An NMR spectrum is a graphical output, where an absorption signal is read upwards from the baseline. The reference point on the horizontal scale is set to zero on the right, and the scale increases to the left. Figure 0509 shows general ranges, according to structural features, where carbon signals appear in ^{13}C-NMR spectra (top) and where hydrogen signals appear in ^{1}H-NMR spectra (bottom).

Figure 0509

General features of ^{13}C-NMR and ^{1}H-NMR spectra.



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The features of NMR spectra (Figure 0509) are:

(1) the number of major signals– this is simple counting; the number of signals in the ^{13}C-NMR spectrum corresponds to the number of nonequivalent carbon sets in the molecule, and the number of signals in the ^{1}H-NMR spectrum corresponds to the number of nonequivalent hydrogen atom groups. In the top spectrum, two ^{13}C-NMR signals (the absorption peaks) are indicated, and in the lower spectrum, two ^{1}H-NMR signals (the absorption peaks) are also indicated.

Interpretation: There are two equivalent groups of carbon atoms and two equivalent groups of hydrogen atoms.

(2) the relative areas of the signals (in ^{1}H-NMR)– the relative areas (not just the heights) of the signals in the ^{1}H-NMR spectrum gives the relative ratio of the number of hydrogen atoms in the groups. You might recall from calculus that the area under a curve is called integration, and so these ratios, measured by comparing the relative areas under these signals, is called the integration of the spectrum. The information is either printed out with the spectrum, as provided in the figure, or can be easily measured by an additional line on the graphical output called the integral (examples below).

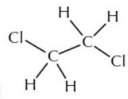
Interpretation: The two equivalent groups of hydrogen atoms are in a 3:1 ratio.

(3) the position of the signals– the left-right position of a signal on the horizontal axis is call its chemical shift and is measured in δ ppm ("delta parts per million") units relative to an internal standard added to the sample. This internal standard is tetramethylsilane (TMS) which is assigned a value of 0 ppm. In general, the higher the value of the chemical shift, the closer the atom group is to a source of electronegativity. The typical scale for a ^{13}C-NMR spectrum is δ 0–220 ppm, while the typical scale for a ^{1}H-NMR spectrum is δ 0–12 ppm. There is a general trend for atoms that are closer to sources of electronegativity to have a higher chemical shift. Thus, sp^2 carbons doubly bonded to electronegative atoms are far to the left (high chemical shift) in the ^{13}C-NMR spectrum, and a hydrogen on such a carbon is far to the left (high chemical shift) in the ^{1}H-NMR spectrum. And although sp^3 carbons are on the right-hand side (low chemical shift), as are hydrogen atom groups on sp^3 carbons, the signal for these atoms shifts to the left when electronegative atoms are attached to them. As you can see in Figure 0509, the experimental results on chemical shift are not completely consistent with this generalization. The origins of these other effects are introduced in Appendix 9 (Book C), but the details are not necessary to this introduction.

Interpretation: In the top spectrum, the chemical shifts for two ^{13}C-NMR signals are at δ 170 ppm and δ 60 ppm, with the carbon group at δ 170 ppm being more closely associated with higher electronegativity (hybridization and/or bonding) than the group at d 60 ppm. In the lower spectrum, the chemical shifts for two ^{1}H-NMR signals are at δ 7.5 ppm and δ 3 ppm, with the hydrogen group at δ 7.5 ppm being more closely associated with higher electronegativity than the group at δ 3 ppm.

Returning now to the difference between 1,2-dichloroethane and 1,1-dichloroethane, which is summarized in Figure 0510.

Figure 0510
Summary of data for 1,2-dichloroethane and 1,1-dichloroethane.

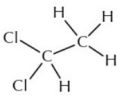


1,2-dichloroethane

molecular formula: $C_2H_4Cl_2$

boiling point = 83 °C
melting point = -35 °C
dipole moment = 1.42 D

number of equivalent carbon atom groups = 1
number of equivalent hydrogen atom groups = 1



1,1-dichloroethane

molecular formula: $C_2H_4Cl_2$

boiling point = 57 °C
melting point = -97 °C
dipole moment = 1.95 D

number of equivalent carbon atom groups = 2
number of equivalent hydrogen atom groups = 2
ratio of hydrogen atom groups = 1:3

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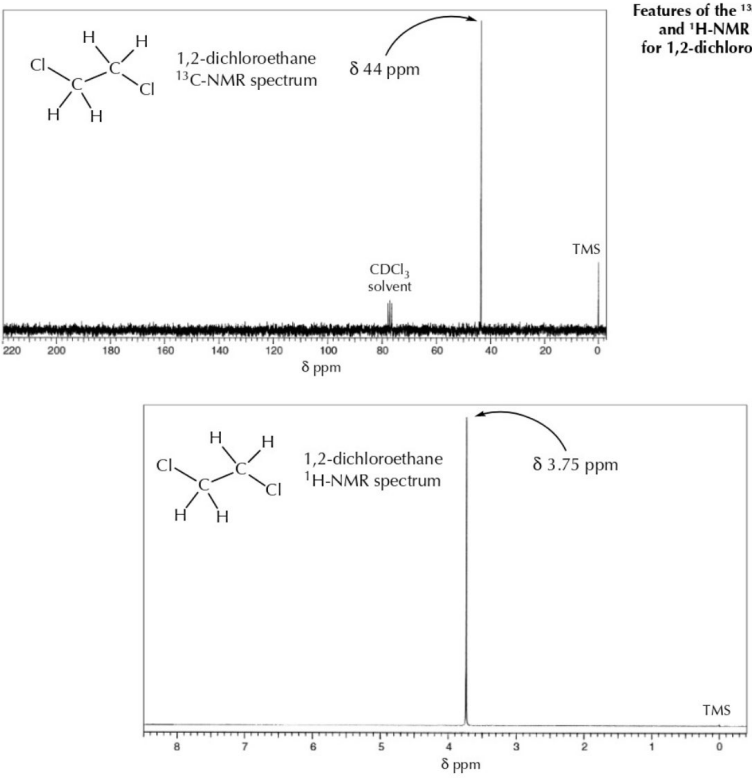
The NMR spectra for 1,2-dichloroethane are shown in Figure 0511.

Figure 0511
Features of the ^{13}C-NMR and ^{1}H-NMR spectra for 1,2-dichloroethane.



This $C_2H_4Cl_2$ isomer has 1 set of equivalent carbon atoms and 1 set of equivalent hydrogen atoms, and so the ^{13}C-NMR and ^{1}H-NMR spectra, respectively, will each show one signal. Because there is only one set of hydrogen atoms, there is no ratio to worry about. The chemical shift for the carbon atom set is δ 44 ppm, read from the scale on the horizontal axis, while the chemical shift for the hydrogen atoms is δ 3.75 ppm. A few other experimental features are indicated. The ^{1}H-NMR and ^{13}C-NMR spectra both show the internal reference (TMS), which marks the δ 0 ppm spot. When deuterium, D (^{2}H), is attached to a carbon, the signal appears as a trio of lines, which is why the ^{13}C-NMR spectrum shows a 3-line signal at δ 77 ppm, attributable to the carbon atom of solvent ($CDCl_3$) in which the spectrum was recorded.

The 1,1-dichloroethane isomer, in contrast, has 2 sets of carbon atoms and 2 sets of equivalent hydrogen atoms in a 3:1 ratio, and so the ^{13}C-NMR and ^{1}H-NMR spectra, respectively, will each show two signals (Figure 0512 on next page).

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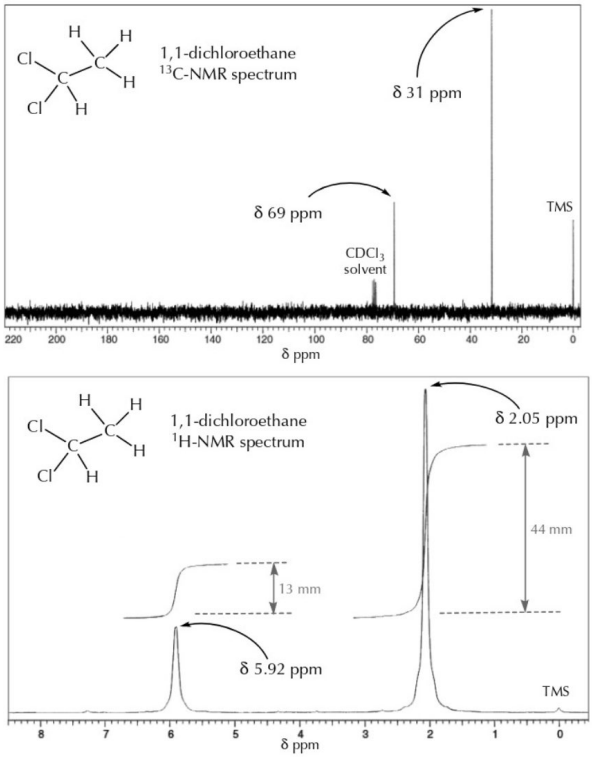
Figure 0512

Features of the ^{13}C-NMR and ^{1}H-NMR spectra for 1,1-dichloroethane.



In the ^{13}C-NMR spectrum, the signal with the higher chemical shift (δ 69 ppm) is carbon atom 1, with the two chlorine atoms attached to it, while the lower chemical shift (δ 31 ppm) is carbon atom 2, with the three hydrogen atoms attached. The relative areas and heights of the ^{13}C-NMR signals does not provide any useful information because of the way the technique is typically performed.

In the ^{1}H-NMR spectrum, the signal with the higher chemical shift (δ 5.92 ppm) is the lone hydrogen atom on carbon atom 1, with the two chlorine atoms attached to it, while the lower chemical shift (δ 2.05 ppm) is the set of 3 hydrogens on carbon atom 2. Those additional s-shaped curves are the integral measurements. The distance between the horizontal plateaus is proportional to the area under the curve (reminder: comparing the peak areas gives the hydrogen atom ratio of the groups, not the peak heights). Thus, the distance between the plateaus at δ 5.92 ppm (measured as a distance 13 mm) compared with the comparable distance measured between the plateaus at δ 2.05 ppm (44 mm) gives a relative area ratio of 13:44 or 1:3 as the closest whole number ratio (hydrogen atoms only come in integers, so the best integer ratio is used, in combination with the fact that the molecular formula indicated a total of 4 hydrogen atoms!).

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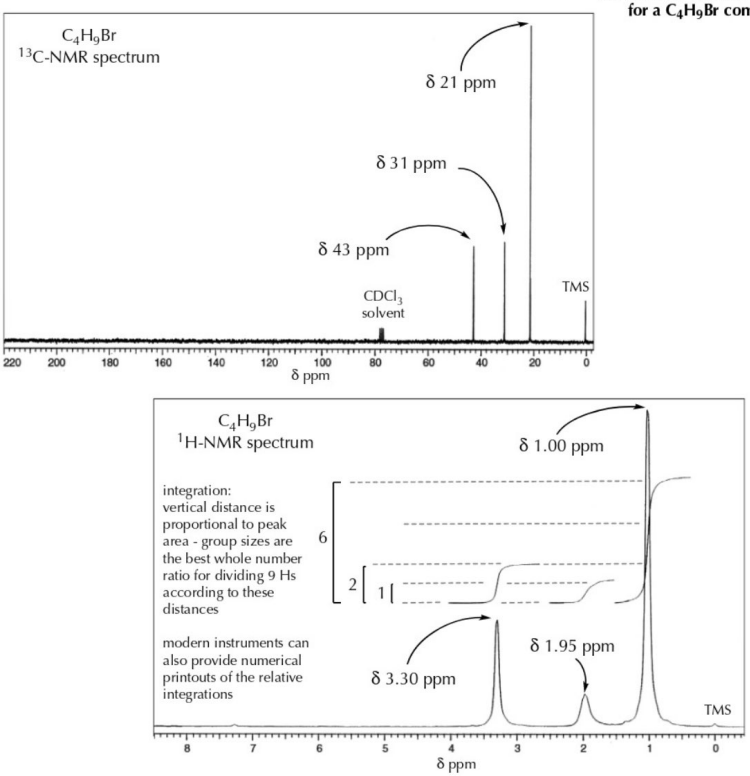
It is important to recognize that the graphical spectra are providing the same information about molecular symmetry as in the analyses in the previous section, namely, the number of nonequivalent sets of carbon and hydrogen atoms in addition to the relative ratios in the hydrogen atom sets. Chemical shift provides a little more information because it tells you about the relative proximity of these sets to sources of electronegativity in the structure. Figure 0513 shows the information you might be faced with in a laboratory situation.

Figure 0513

^{13}C-NMR and ^{1}H-NMR spectra for a C_4H_9Br compound.


C4H9Br
13C-NMR spectrum
δ 21 ppm
δ 31 ppm
δ 43 ppm
CDCl3 solvent
TMS
220 200 180 160 140 120 100 80 60 40 20 0
δ ppm
C4H9Br
1H-NMR spectrum
δ 1.00 ppm
integration: vertical distance is proportional to peak area - group sizes are the best whole number ratio for dividing 9 Hs according to these distances
6
2
1
modern instruments can also provide numerical printouts of the relative integrations
δ 3.30 ppm
δ 1.95 ppm
TMS
8 7 6 5 4 3 2 1 0
δ ppm

Experimentally, you would know the molecular formula of an unknown compound (C_4H_9Br) from a technique called mass spectrometry, and you have also obtained the ^{13}C-NMR and ^{1}H-NMR spectra.

From the molecular formula, you know that the molecule is completely saturated (no units of unsaturation), and that it is an alkyl bromide. The ^{13}C-NMR spectrum shows three absorption signals at δ 43, 31, and 21 ppm, indicating that the 4 total carbons are in three sets (so two of them are equivalent to one another). The ^{1}H-NMR spectrum also shows 3 absorption signals at δ 3.30, 1.95, and 1.00 ppm. Knowing

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that there are 9 total hydrogen atoms is important, because there are finitely few ways to divide 9 hydrogens into three groups. Moreover, the integral lines must represent whole number ratios. You can measure these, but sometimes it is easier to do an "eyeball estimate" rather than get crazy about the detailed numerical values. For example, the ratio is clearly not 3:3:3 because those three plateau-to-plateau measures are not equal. Comparing the ones at δ 3.30 and 1.95 ppm, the ratio looks to be 2:1 (and is clearly neither 1:1 nor 3:1). In contrast, the comparison between the ones at δ 3.30 and 1.00 ppm does look like it is 1:3. Taken together, there is only one way to divide up the 9 hydrogen atoms to satisfy these ratios, and that is (reading left to right), 2:1:6.

Please note that doing this analysis has much more to do with a graphical reasoning puzzle than it does organic chemistry. The task was: how to divide 9 things into three groups with the best whole number ratio indicated by the integral lines.

Taken together, then, the data about this unknown compound is restated in Figure 0514 along with a set of steps that might be used to solve the structure.

Figure 0514

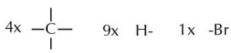
Structural analysis of an unknown C_4H_9Br isomer.

experimental data for an unknown

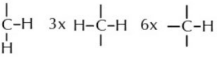
molecular formula: C_4H_9Br

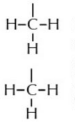
# of equivalent carbon atom groups = 3 ◄---------- interpretation of ^{13}C-NMR spectrum
# of equivalent hydrogen atom groups = 3 ◄---------- interpretation of ^{1}H-NMR spectrum
ratio of hydrogen atoms is 1:2:6 ◄---------- integration of ^{1}H-NMR spectrum

step 1. the pieces:

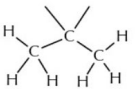


step 2. a set of 6 hydrogens can be

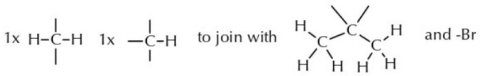




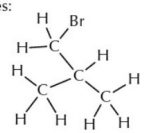
is the only way to do it with this limited set of atoms; they also need to be attached to the same carbon atom because there are not enough atoms for them to be separated from each other



step 3. from C_4H_9Br, the set of 6 hydrogen atoms consumed 3 carbons, which leaves 2 Cs and 3 Hs unaccounted for. With 3 total carbon atom groups, each of these remaining two must be unequivalent, and there are two more hydrogen atom groups [1:2 ratio], which means:



step 4. there is only one way to assemble these pieces:



1-bromo-2-methylpropane

cross-check this with the actual ^{13}C-NMR spectral data: 3 groups of carbons

cross-check this with the actual ^{1}H-NMR spectral data: 3 groups of hydrogens, ratio [2:1:6], the group of 2 is closest to the electronegative bromine atom (highest chemical shift), then the group of 1, then the group of 6

The unknown has a saturated molecular structure with a molecular formula of C_4H_9Br. The structure comprises three sets of carbon atoms with different distances from the source of electronegativity. The 9 hydrogen atoms appear in three sets, also: a set of 2 that is closest to the source of electronegativity, a set of 1 that is next closest, and then an equivalent set of 6 that is farthest way.

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Step 1. All the pieces—4 carbons, 9 hydrogens, and a bromine

Step 2. As in a prior example, the equivalent set of 6 hydrogen atoms is best represented by two CH_3 groups, which also need to end up equivalently placed in the final structure. This leaves 2 carbons that are nonequivalent and two sets of hydrogen atoms (2 in one set and 1 in the other).

Step 3. Following from step 2, there is a CH_2 group and a CH group, which accounts for all of the carbon and hydrogen atoms. There are a couple of ways to piece these together, but the chemical shifts in the ^{1}H-NMR spectrum provides the next best clue: The set of 2 hydrogen atoms is closest to the source of electronegativity, then the set of 1, then the equivalent set of 6 hydrogen atoms.

Step 4. Following the prescription in step 3, the proposed structure is 1-bromo-2-methylpropane, which is consistent with the data (check the proposed structure against the spectra).

In summary, nuclear magnetic resonance spectroscopy is a powerful experimental tool for structural analysis, and gives us, in this introduction to the technique, three useful pieces of information about the connectivity of a molecule:

1. The number of different signals in the carbon or proton nuclear magnetic resonance spectrum of the compound gives us information about the symmetry of the molecule and the equivalence or nonequivalence of the different atoms there.

2. The integration of the proton nuclear magnetic resonance spectrum tells us the relative numbers of hydrogen atoms at each chemical shift.

3. The chemical shifts of the signals tell us about the environment in which the carbon and hydrogen atoms exist, especially whether any strongly electronegative atoms are close by.

The NMR experiments can also provide other useful information. For example, the ^{1}H-NMR spectrum provided for 1,1-dichloroethane in Figure 0512 was recorded under low-resolution conditions and shows relative broad and nondescript absorption peaks. In the more typical high-resolution spectrum of the compound, shown in Figure 0515, the broad signals are seen to be made up of a group of finer lines.

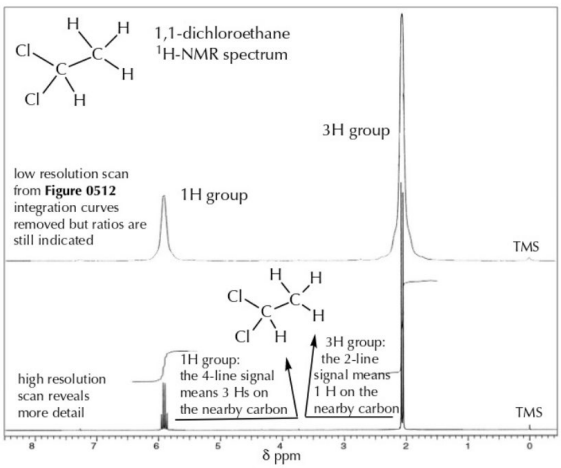

Figure 0515
Low- and high-resolution ^{1}H-NMR spectra for 1,1-dichloroethane.

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This chapter does not include high-resolution ^{1}H-NMR or the guidance on how to interpret the multiline patterns. This introduction is focused on giving you a chance to practice with the three features listed above using low-resolution spectra (number of C and H groups, ratio of H groups, and chemical shift). However, if you encounter other NMR spectra, the multiline patterns give information about how many other hydrogen atoms are nearby in the structure. In the figure, the fine lines and their ratios can be used to count the number of hydrogen atoms that are nearby to the hydrogens that are giving the signal. The 4-line pattern at δ 5.92 ppm, for instance, indicates 3 hydrogen atoms that are on nearby carbon atoms, while the 2-line pattern at δ 2.05 ppm indicates that there is 1 hydrogen atom that is on a nearby carbon. Much more information about interpreting the high-resolution spectra is provided in Appendix 9.

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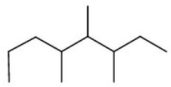
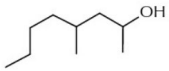
PRACTICE QUESTIONS

5.01 Provide the IUPAC name for these organic molecules.

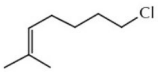
(a)



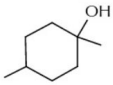
(b)



(c)

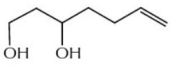


(d)



(e)

(f)



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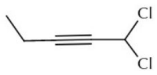
5.01 (cont.) Provide the IUPAC name for these organic molecules.

(g)



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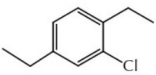
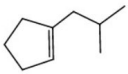
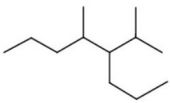


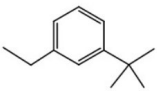
(i)



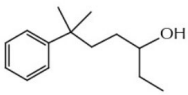
(j)



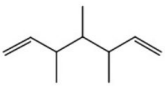
(k)



(l)



(m)



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5.02 Provide the structures for the following organic molecules based on their names.

(a) 2,2,4,4-tetrachlorocyclohexan-1-ol

(b) 1-ethyl-3-isopropylcyclobutane

(c) 1-butyl-2-methylcyclohex-1-ene

(d) cyclopropylbenzene

(e) 7,7-dibromohept-6-en-3-ol

(f) 1-(sec-butyl)-1-methylcyclopentane

(g) 4,4,4-trifluorobut-1-yne

(h) 5,7-diphenylcycloheptane-1,4-diol

(i) 5-chlorocyclohexa-1,3-diene

5.03 Based on the following data, deduce the molecular structure and then provide the IUPAC name for each of the following (reminder: units of unsaturation provides useful structural information).

(a) $C_7H_{14}Cl_2$
2 sets of equivalent carbons
2 sets of equivalent hydrogens
ratio [6:1]

(b) C_3H_7BrO (an alcohol)
3 sets of equivalent carbons
4 sets of equivalent hydrogens
ratio [2:2:2:1]

(b) $C_6H_{12}Br_2$
4 sets of equivalent carbons
2 sets of equivalent hydrogens
ratio [3:1]

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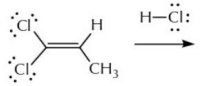
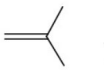
5.04 The following electrophilic addition reactions produce two regioisomeric products in unequal amounts, according to Markovnikov's Rule.
(i) draw and name the expected pair of products
(ii) enter the information from ^{1}H-NMR and ^{13}C-NMR spectroscopy that could be used to identify the products

(a)



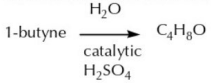
names:				
^{13}C-NMR:		number of equivalent carbon atom groups		number of equivalent carbon atom groups
^{1}H-NMR:		number of equivalent hydrogen atom groups		number of equivalent hydrogen atom groups
		ratio of atoms in the hydrogen atom groups		ratio of atoms in the hydrogen atom groups

(b)



names:				
^{13}C-NMR:		number of equivalent carbon atom groups		number of equivalent carbon atom groups
^{1}H-NMR:		number of equivalent hydrogen atom groups		number of equivalent hydrogen atom groups
		ratio of atoms in the hydrogen atom groups		ratio of atoms in the hydrogen atom groups

5.05 The electrophilic addition reaction of water (H_2O) to 1-butyne takes place under acid-catalyzed conditions. The experimental result is an unexpected product. Here are some experimental data about the reaction outcome. A reminder that units of unsaturation also provides useful information.



(i) C_4H_8O is not an alcohol
(ii) C_4H_8O has 4 carbon groups (^{13}C-NMR)
(iii) C_4H_8O has 3 hydrogen groups (^{1}H-NMR) with a ratio of 3:2:3
(iv) the connectivity of the carbon atom chain is maintained in this reaction

Based on these data, what is the structure of this C_4H_8O product?

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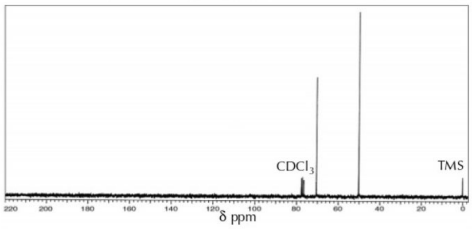
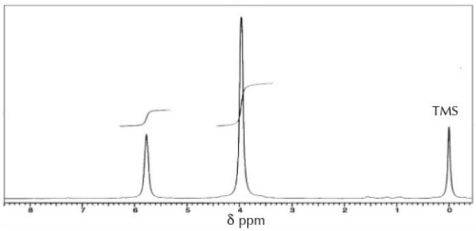
5.06 The ^{1}H-NMR and ^{13}C-NMR spectra for one of the $C_2H_3Cl_3$ isomers are shown here. Deduce the structure and provide a brief explanation for how each of the spectra support the structural assignment.



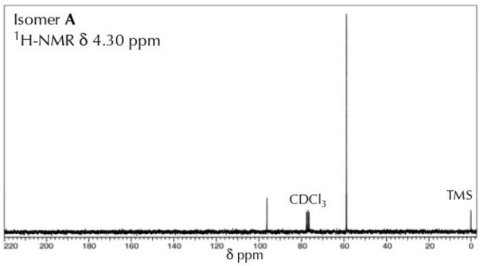


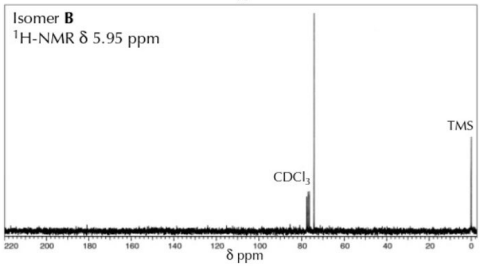
structural assignment

interpretation of ^{13}C-NMR

interpretation of ^{1}H-NMR

5.07 The ^{13}C-NMR spectra for two $C_2H_2Cl_4$ isomers (isomer **A** and isomer **B**) are shown here. They both have only one absorption signal in their ^{1}H-NMR spectra. Isomer **A** has a ^{1}H-NMR signal at δ 4.30 ppm, and isomer **B** has a ^{1}H-NMR signal at δ 5.95 ppm. Deduce the structures and provide a brief explanation for how each of the spectra support the structural assignments.





*isomer **A***

*isomer **B***

comparison of ^{13}C-NMR data

comparison of ^{1}H-NMR data

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5.2 Sources of Stereoisomerism

A. Stereoisomerism

A simple question has driven structural organic chemistry since the early 1800s: Are these two molecules the same or not the same, and if not, how do they differ? Going into the 19th century, the answer was elemental composition. Two substances were different if they had different elemental compositions (molecular formulas).

The observation that different substances (i.e., exhibiting different properties) could have the same elemental composition led chemists to think about connectivity and molecular structure as the way in which two substances could be simultaneously the same (same molecular formula) and not the same (different connectivity). Hence the invention of the word "isomer" (same parts).

By the 1840s, another problem emerged. Substances with the same connectivity were observed to have different properties, and thus must be different molecules. How to have different molecules with the same connectivity presented an incredible intellectual challenge in the mid-19th century. There was no structural theory for molecules (remember, electrons were not discovered until 1900, and the model of the atom did not begin to be accepted until the 1920s). And useful experimental techniques such as NMR spectroscopy were still over a century away.

As summarized briefly in the introductory essay for this chapter, history records that van't Hoff and Le Bel, in 1874, independently proposed that differences in the three-dimensional arrangement of atoms in space could account for the observed differences in properties. They were right, and so molecules with the same molecular formula and the same connectivity that differed in the spatial arrangement of their atoms were eventually called stereoisomers, and the study of the three-dimensional structure of molecules was called stereochemistry.

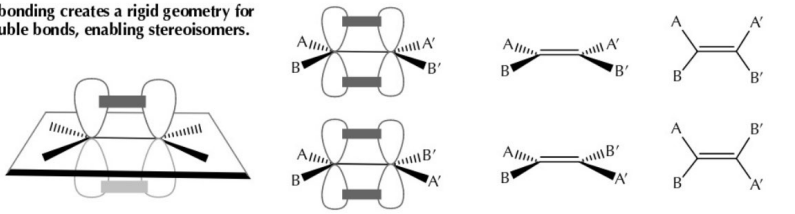
In this text, we will begin with three different sources of stereoisomerism, that is, the structural features that allow you to predict that stereoisomers will exist. There are many more than these three sources, but these three cases provide a solid foundation for understanding any of the others.

B. Double Bonds That Are Unsymmetrically Substituted at Both Ends

Two sp^2 carbon atoms joined together to make a double bond creates a rigid structure. According to our bonding picture, the pi bonding overlap holds all six of the atoms associated with the two trigonal planar geometries as coplanar and fixed in place (Figure 0516).

Figure 0516

Pi bonding creates a rigid geometry for double bonds, enabling stereoisomers.



two trigonal planar atoms are fixed to be coplanar by the pi bond

this creates the possibility that two molecules can have the same connectivity and differ by geometry

drawings in the xz plane for the C=C and two different geometries

drawings in the xy plane for the C=C and two different geometries

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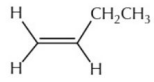
The rigid, rectangular array of atoms in a double bond gives rise to the first possibility of stereoisomerism. For example, among the C_4H_8 structural isomers, there are two molecules with the 2-butene connectivity (Figure 0517). These are the two 2-butene stereoisomers.

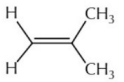
Figure 0517

Because of stereoisomerism, there are four C_4H_8 isomers with double bonds in them.



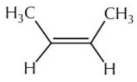
1-butene

boiling point = -5 °C
melting point = -185 C
dipole moment = 0.50 D



2-methyl-1-propene

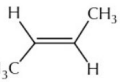
boiling point = -6 °C
melting point = -140 C
dipole moment = 0.34 D



2-butene

cis (same side)
pair of methyl groups
and hydrogen pair
on the double bond

boiling point = 1 °C
melting point = -139 C
dipole moment = 0.30 D



2-butene

trans (opposite side)
pair of methyl groups
and hydrogen pair
on the double bond

boiling point = 2.5 °C
melting point = -106 C
dipole moment = 0.00 D

As illustrated in the figure, these compounds are indeed different, possessing different physical properties. The relative spatial position of the two methyl groups is either diagonal to one another (on opposite sides of the double bond, called the trans relationship) or on the same side as one another (called the cis relationship). These same terms, trans and cis, are used to describe any of the opposite- and same-sided relationships, so the spatial relationship between the lone hydrogen atoms attached to each end, for instance, can also be said to be trans or cis. Note that the nomenclature system for a molecular structure does not account for any difference in geometry, and both of the 2-butene molecules have the same name because they have the same connectivity. To differentiate them, a geometrical label is needed (below).

Not every molecule containing a double bond has stereoisomers. A double bond needs to have different substituent groups at both ends for stereoisomers to be possible, in which case two (and only two) different fixed spatial arrangements are possible. The other C_4H_8 structural isomers with double bonds in Figure 0517, 1-butene and 2-methyl-1-propene, have at least one end atom of the double bond where the substituents are identical, and so these connectivities are unique and do not represent structures that have possible stereoisomers.

Double bonds in rings are a special case when it comes to having stereoisomers. Because of bond angle constraints, double bonds in small rings (less than 8 atoms) typically have only one stable geometry because it is difficult to impossible to wrap the atoms of the ring around into a trans relationship (you are strongly encouraged to try building molecular models of these compounds; you will see how difficult it is to form some of these shapes). Although all of the double bonds in Figure 0518 on the next page meet the criterion of having a different pair of groups at both ends, cyclooctene is the first cyclic alkene in this series where both of the stereoisomers are observable and isolable.

The existence of stereoisomers creates a new naming problem. Stereoisomers have the same connectivity (both of the molecules in Figure 0517 are named 2-butene), so a system of identifying and naming geometry is needed. For many years, the terms "cis" and "trans" were also used as the geometrical labels, appearing in front of the connectivity (*cis*-2-butene and *trans*-2-butene). The cis/trans system of labeling geometries was not created with systematic rules, and ambiguities resulted in trying to name more complex molecules where the groups being referenced as "cis" or "trans" was not as obvious as in the 2-butene stereoisomers. In 1968, the "cis" and "trans" system of assigning geometrical labels in names was replaced by a more reliable one that uses the letters "Z" and "E" after assigning relative priorities to the groups at each end.

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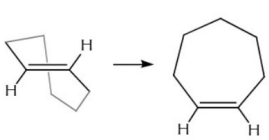
Figure 0518

Small ring cycloalkenes have only one stable geometry for their double bonds.

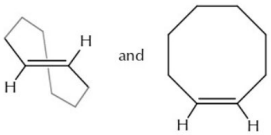
cyclopropene cyclobutene cyclopentene cyclohexene

these cis ring geometries are the only stable forms



cycloheptene

the trans ring geometry breaks at 1 °C with a half-life of 10 minutes (estimated activation energy 17 kcal/mol)

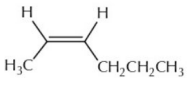


cyclooctene

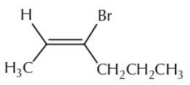
trans ring geometry	*cis ring geometry*
boiling point = 143 °C	boiling point = 145-6 °C
melting point = -59 °C	melting point = -16 °C
dipole moment = 0.82 D	dipole moment = 0.43 D

Figure 0519

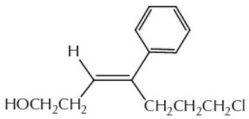
Representative double bonds and their names (based on rules in Appendix 4).



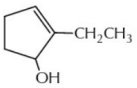
(*Z*)-2-hexene
also OK:
cis-2-hexene



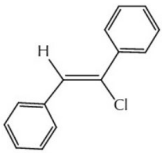
(*E*)-3-bromo-2-hexene
historical (not used today):
cis-3-bromo-2-hexene



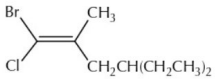
(*E*)-7-chloro-4-phenylhept-3-en-1-ol
or
(*E*)-7-chloro-4-phenyl-3-hepten-1-ol



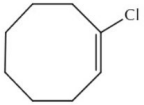
2-ethyl-2-cyclopenten-1-ol
or
2-ethylcyclopent-2-en-1-ol
(it is "Z", but no geometry needed for the small ring)



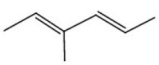
(*Z*)-1-chloro-1,2-diphenylethene
historical (not used today):
trans-1-chloro-1,2-diphenylethene



(*E*)-1-bromo-1-chloro-4-ethyl-2-methyl-1-hexene
or
(*E*)-1-bromo-1-chloro-4-ethyl-2-methylhex-1-ene



(*E*)-1-chlorocyclooct-1-ene
historical (not used today):
cis-1-chlorocyclooct-1-ene



(2*E*, 4*E*)-3-methyl-2,4-hexadiene
or
(2*E*, 4*E*)-3-methylhexa-2,4-diene

2-bromo-1,3-cyclohexadiene
or
2-bromocyclohexa-1,3-diene

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An introduction to assigning these priorities and then naming stereoisomers is presented in Appendix 4. The "Z/E" system is applicable to any double bond that meets the criterion of having a different pair of groups at both ends and can always be used. You may encounter older resources that use "cis" and "trans," and so you should understand that these are not identical terms. IUPAC still permits the optional use of "cis" and "trans" as geometrical labels, but only when a pair of hydrogen atoms is being compared. Some examples of the double bond geometries you should be able to label as "E" or "Z" are presented in Figure 0519, including a few cases where "cis" and "trans" are permitted, as well as cases where those terms have been abandoned. The labels "E" and "Z" come from German words, so an amusing mnemonic that students are fond of using puts all the hissing "letter z" sounds together: the label "Z" is when the two high priority groups are "zis" (on "zee zame zide").

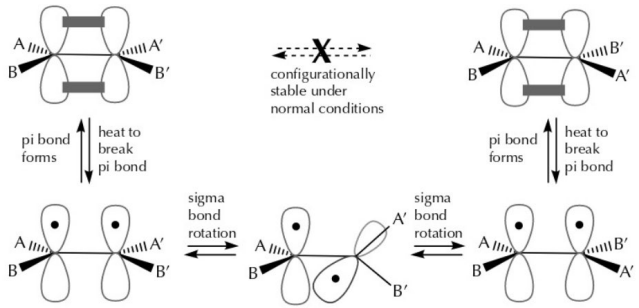
Two important and commonly encountered concepts in stereochemistry are "configuration" and "stereogenic atom."

Configuration. The term "configuration" refers to a geometrical arrangement that is stable and observable under normal human/experimental conditions. Pure samples of the "E" and "Z" forms of 2-butene will retain their geometries indefinitely at normal room temperature unless deliberately acted upon with the intent to change them. (*E*)-2-butene and (*Z*)-butene are said to be configurationally stable under normal laboratory conditions.

Under extreme conditions, the geometries might not be stable. Heating either of these molecules to a high enough temperature, for example, could provide enough energy to break the pi bond, resulting in the molecule rotating around its central sigma bond, and enabling the molecule to reform in both the "E" and "Z" forms. The molecule would have no memory of where it started (Figure 0520).

Figure 0520

"E" and "Z" double bonds are generally configurationally stable under normal experimental conditions.



Most often, the word "configuration" refers to a fixed and observable geometry under typical experimental conditions. Some phrases where the term is used might include:

What is the configuration (or stereochemical configuration) of that double bond, "E" or "Z"?

That double bond has configurational stability.

The double bond in that small ring has only one possible configuration.

Which configuration formed as the major stereoisomer in that reaction?

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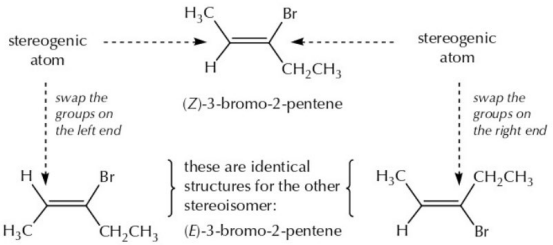
Stereogenic Atom. The term "stereogenic" means "source or origin of stereoisomerism," and a "stereogenic atom" is one that is responsible for the existence of stereoisomers in a molecular structure. Conceptually, the test for a stereogenic atom is whether switching any two substituent groups creates a stereoisomer relative to the original positions of the groups. Both ends of a double bond having a different pair of groups at both ends qualify as stereogenic atoms. If you start with the (*Z*)-stereoisomer of 3-bromo-2-pentene (Figure 0521), you can swap the substituent groups (just redrawing, not a chemical process) and create the single other stereoisomer, the (*E*)-3-bromo-2-pentene, and vice versa. There are only ever two, and only two, stereoisomers from this single source of stereoisomerism.

Figure 0521

The ends of "E" and "Z" double bonds are stereogenic atoms.


stereogenic atom
stereogenic atom
swap the groups on the left end
swap the groups on the right end
(Z)-3-bromo-2-pentene
these are identical structures for the other stereoisomer:
(E)-3-bromo-2-pentene

Conclusion: Double bonds that are unsymmetrically substituted at both ends represent a connectivity for which two stereoisomers exist, and these different molecules carry the geometrical labels "*Z*" and "*E*" (or in special cases, "*cis*" and "*trans*"). Double bonds in small rings, however, can exist in only one stable configuration, and the use of geometrical labels is not necessary.

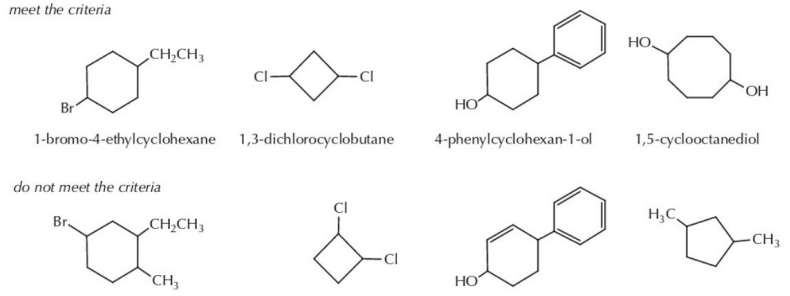
C. Symmetrical Rings with an Even Number of Atoms and Substituted at Opposite Vertices

The second example of a source of molecular stereoisomerism is quite narrowly defined: symmetrical rings with an even number of atoms in the ring and substituted only at opposite vertices. Understanding this category is most easily achieved by considering a set of examples where all of the criteria are met and comparing them with examples where at least one criterion is not met. Figure 0522 contains a set of examples for your consideration. Notice that two pathways, from one of the substituents to the other, must be identical for a molecular to fit into this category. The third example in the second row of Figure 0522 (4-phenylcyclohex-2-en-1-ol) does not meet the symmetrical criterion because one pathway from the

Figure 0522

Assessing ring symmetry.

Representative examples that do and do not meet the criteria: symmetrical rings with an even number of atoms and substituted at opposite vertices.



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hydroxyl group to the phenyl group contains a double bond, and the other pathway along the 6-membered ring does not.

All of the rings that meet the symmetrical/even-numbered/oppositely substituted criteria have a strong geometrical analogy with double bonds. The six atoms on the opposite vertices are all in the same plane, with two equivalent strands of atoms connecting them. Using standard line, dash, and wedge representations, the two ring atoms sitting at these opposite vertices are stereogenic atoms. And as with double bonds, molecules meeting these criteria represent connectivities with two (and only two) stereoisomers (Figure 0523), and the substituent groups on different atoms can be referred to as being cis and trans to one another around the perimeter of the ring.

Sometimes, naming these two geometries is comparable to naming double bond configurations: When a pair of hydrogen atoms is being compared, the same geometrical labels (*cis*- and *trans*-) can be used. However, the geometrical labels "E" and "Z" are not used with molecules in this category.

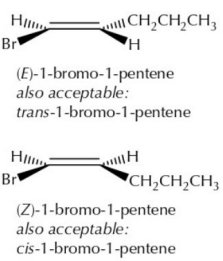
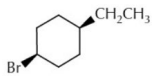


Figure 0523
Two stereoisomers result from molecules having symmetrical rings with an even number of atoms, and substituted at opposite vertices

As presented in detail in Appendix 3 (Book B), stereoiomers in this category need to use "r" and "s" geometrical labels on their stereogenic atoms when "cis" and "trans" cannot be assigned based on a pair of hydrogen atoms. Figure 0524 includes examples of molecules in the symmetrical/even-numbered/oppositely substituted ring category that can and cannot be named using the "cis" and "trans" labels.

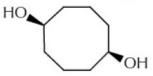
Figure 0524
Stereoisomers that can and cannot be named using "cis" and "trans."

can be named using "cis-" or "trans-" labels



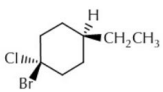
cis-1-bromo-4-ethylcyclohexane
uses the geometrical label (1*s*, 4*s*)-,
see Appendix 3 for more details

trans-1,3-dichlorocyclobutane
uses the geometrical label (1*r*, 3*r*)-,
see Appendix 3 for more details

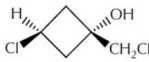


cis-1,5-cyclooctanediol
uses the geometrical label (1*s*, 5*s*)-,
see Appendix 3 for more details

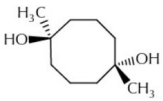
cannot be named using "cis-" or "trans-" labels



1-bromo-1-chloro-4-ethylcyclohexane
uses the geometrical label (1*s*, 4*s*)-,
see Appendix 3 for more details



3-chloro-1-ethylcyclobutan-1-ol
uses the geometrical label (1*r*, 3*s*)-,
see Appendix 3 for more details



1,5-dimethyl-1,5-cyclooctanediol
uses the geometrical label (1*r*, 5*r*)-,
see Appendix 3 for more details

Examples of stereoisomers with symmetrical rings and an even number of atoms, with substituents at opposite vertices, which can and cannot be named using "cis" and "trans."

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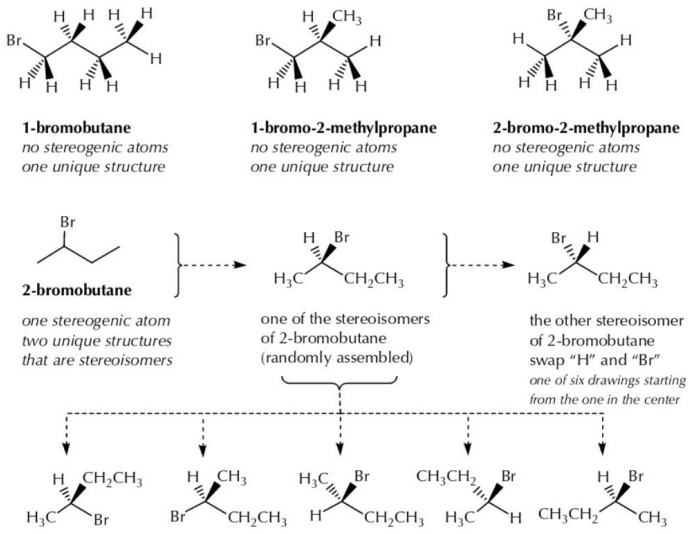
Conclusion: Symmetrical rings with an even number of atoms and substituted at opposite vertices represent a connectivity for which two stereoisomers exist, and these different molecules can carry the geometrical labels "cis-" and "trans-" when a pair of hydrogen atoms is being compared.

D. Tetrahedral Atoms with Four Different Substituents

The third example (of three) in this introduction to sources of stereoisomerism is a tetrahedral atom with four different substituent groups attached to it. As with the other two examples, these atoms are stereogenic, creating two (and only two) stereoisomers. Unlike the other two examples, however, truly understanding these three-dimensional arrangements (and this topic) requires you to have a rock-solid understanding of the tetrahedral arrangement in the physical world, and how we represent it as drawings on two-dimensional surfaces. This understanding also requires a certain degree of mental flexibility for visualizing the drawings of a tetrahedron, or other objects, being rotated or reoriented on a two-dimensional surface. A couple of molecular models of tetrahedral atoms with four different groups attached would be exceedingly useful to you right now, regardless of your prior skills or experience with such visualizations.

Figure 0525

Stereochemical analysis for the three C_4H_9Br structural isomers: two of them have unique structures, while the 2-bromobutane connectivity represents two (and only two) 2-bromobutane stereoisomers.



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There are four different structural isomers (connectivities) for C_4H_9Br (1-bromobutane, 2-bromobutane, 1-bromo-2-methylpropane, and 2-bromo-2-methylpropane), each of which contains four tetrahedral carbon atoms. Only 2-bromobutane contains a tetrahedral atom that is also a stereogenic atom, because only carbon 2 of this isomer has four different groups attached to it (Figure 0525). This means there are two stereoisomers of 2-bromobutane, while the other three C_4H_9Br structural isomers do not have stereoisomers.

The stereogenic atom in 2-bromobutane has been classified a few different ways over the years. Historically, these types of stereogenic atoms were called "asymmetric centers" or "chiral centers," and the latter term is still in common use today. We will define the meaning of this term "chiral" in the next section. This tetravalent, tetrahedral stereogenic atom is also commonly called a "chiral stereocenter," "a center of chirality," a "tetrahedral stereocenter," or just a "stereocenter," with the implicit understanding that it means a tetrahedral atom with four different groups attached to it. In this text, we will most often use the term "stereocenter" to refer to these tetravalent atoms with four different groups, and sometimes include a modifier such as in "tetrahedral stereocenter" and "chiral stereocenter" so that you see these terms. As in the first sentence of this paragraph, we are making the distinction between one of these specific tetrahedral stereocenters and the broader term, stereogenic atom, which refers to any atom from which switching two groups creates stereoisomers.

One reliable way to draw the two stereoisomers of 2-bromobutane is to start with one of them drawn at random; there are only two of them, after all. By placing the four groups around a tetrahedral carbon, you know that one of the two stereoisomers has been drawn (Figure 0525). Then, using the definition of a stereogenic atom, exchanging two of the groups will create the other stereoisomer. Which two? Any pair will do—it does not matter—and you should prove this to yourself with models. This statement (any pair will do) is important because it means, starting with one drawing of a random tetrahedral arrangement, that there are six different swaps that might be drawn, and all of these different-looking drawings actually represent the single, other three-dimensional arrangement that is possible. That is: The drawing of the other stereoisomer is a different molecule of 2-bromobutane compared with the original. Moreover, if you start with any one of these six drawings of the second stereoisomer and recall that there are two (and only two) arrangements, then swapping any two groups on any of these six drawing must, by definition, recreate the original three-dimensional arrangement.

You are encouraged in the strongest possible terms to try this exercise with some models. Start with two tetrahedral centers that have four different groups and make two exact copies of the same three-dimensional arrangement. Prove to yourself that they are identical by trying to make them overlap and seeing that they do. Then take one of them and swap any two of the groups. You have now made an arrangement that is different, and it cannot be overlapped on the original. Now take that second one and switch two more groups; you have remade the original and you should be able to prove that.

The mental gymnastics required to keep all of this straight using drawings are challenging until you get more experience. The logic of stereogenic atoms is helpful: There are two (and only two) arrangements. Learning how to label the two tetrahedral geometries gives you an exact method for making comparisons. Assigning the geometrical labels, which are "R" and "S," derives from a 4-step technique (Figure 0526 on the next page).

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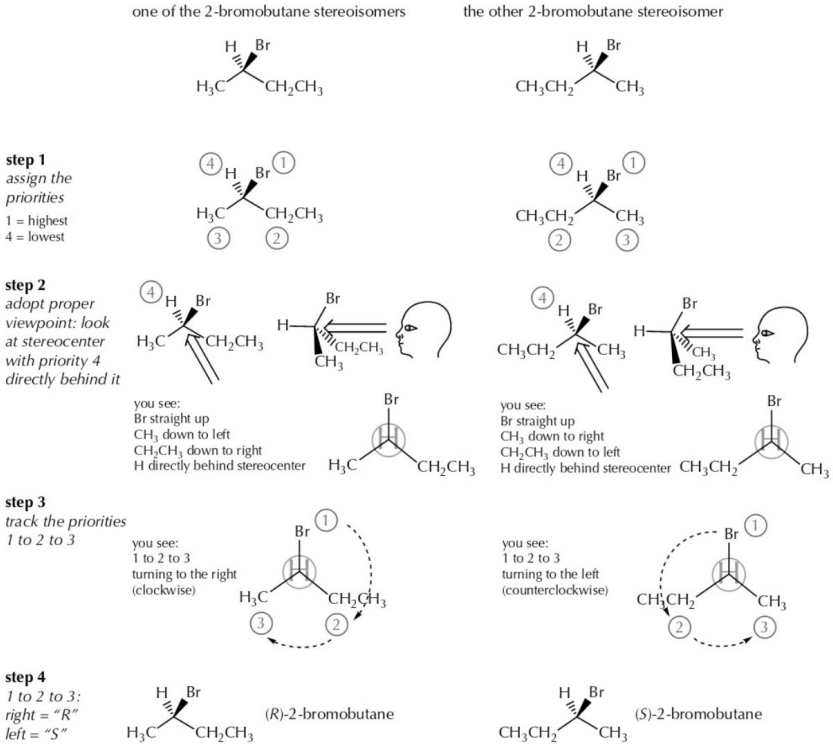
Figure 0526

Assigning the geometrical labels "R" and "S" to a tetrahedral stereocenter.



Step 1. Assign the priorities to the four substituent groups (1=highest, 4=lowest) using the Cahn-Ingold-Prelog Rules (Appendix 3).

Step 2. Adopt the point of view so that you are looking directly at the three-dimensional stereogenic atom (not the flat drawing) with the bond to lowest priority group pointed away from you (this is extremely easy to do with a physical model, so do it).

Step 3. Starting from this point of view, the way your eyes track as you go from priority 1 to priority 2 to priority 3 will turn in one of two (and only two) directions, a turn to the right (clockwise) or a turn to the left (counterclockwise).

Step 4. As viewed from this point of view, the one with the clockwise 1-to-2-to-3 arrangement is given the geometrical label "R" (from the Latin term *rectus*, meaning "right," as in correct or normal), and the one with the counterclockwise 1-to-2-to-3 arrangement is given the geometrical label "S" (from the Latin term *sinister*, meaning "to the left," the evil and unlucky direction).

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Of these 4 steps, the second one is the rule that new learners get wrong or even try to ignore, and it is (by far) the most critical. The incidental, random placement of the substituent groups in a two-dimensional drawing is not a three-dimensional visualization, so only studying the placement of priorities 1 through 3 without taking the required three-dimensional point of view into consideration means you are ignoring one of the steps used to define the labels. There are two common strategies used to help interpret the three-dimensional structure when faced with the two-dimensional drawings.

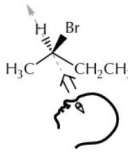
Strategy I: location of the priority 4 substituent on the dash, wedge, or one of the lines (no redrawing)

Fortunately, in all of the different drawings you might make for a tetrahedral stereocenter, the lowest priority group can only end up in one of three positions: on the dash, on the wedge, or on one of the lines, and this means there are really three distinct cases for visualizing the geometry of a tetrahedral stereocenter and generating the correct "R" or "S" label (Figure 0527).

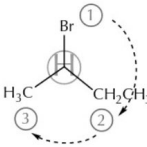
Figure 0527

Assigning the geometrical labels "R" and "S" based on location of the priority 4 substituent (no redrawing).

Case 1: priority 4 on the dashed line, behind the plane of the drawing surface



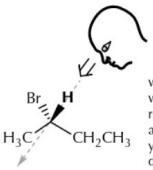
with the H on the dashed line, the remaining groups appear positioned as you see them in the drawing with the proper perspective



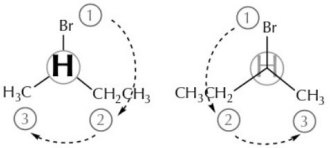
you can simply assign the geometry label based on what you see, as the perspective is correct, and 1 to 2 to 3 is "R"

(*R*)-2-bromobutane

Case 2: priority 4 on the wedge line, above the plane of the drawing surface



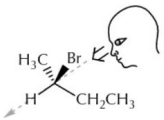
with the H on the wedge line, the remaining groups appear positioned as you see them in the drawing are in the wrong perspective because priority 4 is pointed at you



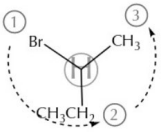
from the perspective of the drawing as you look at it, 1 to 2 to 3 looks clockwise, but you need to be behind the page, looking forward, to have the defined perspective for the label, so either (a) reverse the rules or (b) adopt the proper perspective; either way, this geometry is "S"

(*S*)-2-bromobutane

Case 3: priority 4 on a line in the plane of the drawing surface



with the H on a plain line, you need to imagine yourself in the plane of the drawing surface, looking at the stereocenter with the priority 4 group directly behind it



with your face pressed sideways in the drawing plane, the ethyl group is now straight down, the bromine is up to your left, and the methyl up to your right

(*S*)-2-bromobutane

Case 1 (lowest priority group on the dash): from this point of view, the low priority group is basically in the proper position, pointed away from the viewer as you look at the stereogenic atom; the visualization of the tetrahedron follows from the two-dimensional drawing

Case 2 (lowest priority group on the wedge): from this point of view, the low priority group is exactly opposite from the viewpoint defined for making the assignment of the label, pointed towards the viewer as you look at the stereogenic atom; so the visualization of the tetrahedron needs to be from the exact opposite side of the imagined shape, from the back side of the writing surface

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(another common interpretation of this case is that, with the lowest priority group pointed towards the viewer instead of away, the apparent definitions of clockwise and counterclockwise are reversed, so a clockwise turn from this perspective is actually counterclockwise from the other side of the bond)

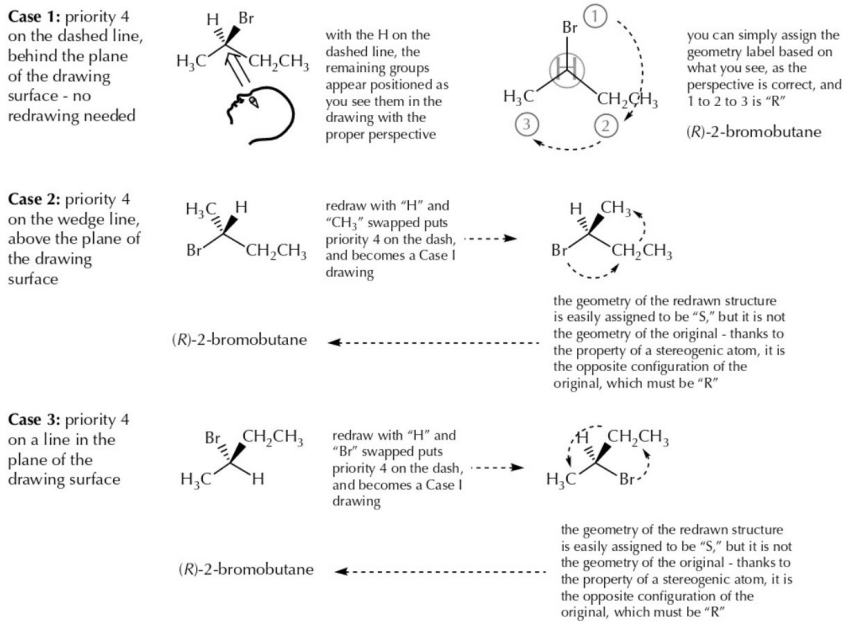
Case 3 (lowest priority group on one of the lines): from this point of view, the viewer's perspective can be exactly defined by imagining the extension of the bond axis from the priority 4 group, through the stereogenic center, and to the viewer's eye; this point of view is also shown in the drawings that defined "R" and "S," earlier, in Figure 0526

Strategy II: relocate the priority 4 substituent to the dash (with redrawing)

This strategy relies on the definition of a stereogenic atom. Because swapping any two groups at a stereogenic atom creates the other stereoisomer, an "R" geometry can be converted to an "S" geometry by this exchange. Given the ease of visualization described in Strategy I (Case 1), with the lowest priority group on the dashed line, any of the other arrangements (Cases 2 and 3) can be converted into Case 1 by swapping the low priority group with the group on the dashed line. Because doing this exchange changes the geometrical label, if the redrawn swapped form is an "S" geometry, then the original was an "R," and vice versa (Figure 0528).

Figure 0528

Assigning the geometrical labels "R" and "S" based on relocating the priority 4 substituent to the dashed line (with redrawing).


Case 1: priority 4 on the dashed line, behind the plane of the drawing surface - no redrawing needed
with the H on the dashed line, the remaining groups appear positioned as you see them in the drawing with the proper perspective
you can simply assign the geometry label based on what you see, as the perspective is correct, and 1 to 2 to 3 is "R"
(R)-2-bromobutane
Case 2: priority 4 on the wedge line, above the plane of the drawing surface
redraw with "H" and "CH3" swapped puts priority 4 on the dash, and becomes a Case I drawing
the geometry of the redrawn structure is easily assigned to be "S," but it is not the geometry of the original - thanks to the property of a stereogenic atom, it is the opposite configuration of the original, which must be "R"
(R)-2-bromobutane
Case 3: priority 4 on a line in the plane of the drawing surface
redraw with "H" and "Br" swapped puts priority 4 on the dash, and becomes a Case I drawing
the geometry of the redrawn structure is easily assigned to be "S," but it is not the geometry of the original - thanks to the property of a stereogenic atom, it is the opposite configuration of the original, which must be "R"
(R)-2-bromobutane

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If the lowest priority group is on the dashed line, then no redrawing is needed because this vewipoint is a repeat of Strategy I (Case 1); the low priority group is in the proper position, pointed away from the viewer as you look at the stereogenic atom, so the visualization of the tetrahedron follows from the two-dimensional drawing.

If the lowest priority group is on the wedge or on one of the lines, then redraw the molecule in exactly the same orientation with that group swapped for the group on the dashed line; this now becomes the same case as above, and if the geometry of the redrawn molecule is "R," then the original geometry in question was "S" (and vice versa).

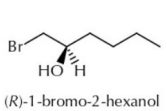
Figure 0529 contains a few examples of some fully named molecules. You should affirm your agreement with these names, and practice with the different strategies for assigning the geometrical labels.

One last strategic note: If you are called upon to draw a specific stereoisomer of a molecule, you might spend a lot of needless time trying to get it just right in one attempt. It is far easier to just make a guess, assign the geometrical label for the drawing you made, and then correct what needs to be corrected. Because a stereocenter can only be "R" or "S," you have a 50:50 chance of drawing it correctly in the first place. If you guessed wrong, you can readily change an "R" geometry into an "S" geometry by applying the stereogenic principle of swapping any two groups. Two examples of this strategy are also shown in Figure 0529, where you need to generate a structure from a name rather than generating a name from a structure.

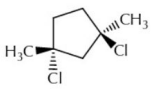
Conclusion: Tetrahedral atoms with four different substituent groups represent a connectivity for which two stereoisomers exist, and these different molecules carry the geometrical labels *R*- and *S*-.

Figure 0529

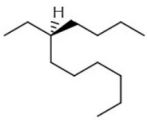
Named examples of stereoisomers with tetrahedral stereocenters.



(*R*)-1-bromo-2-hexanol
or
(*R*)-1-bromohexan-2-ol



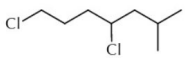
(1*R*, 3*R*)-1,3-dichloro-1,3-dimethylcyclopentane



(*S*)-5-ethylundecane

drawing a specific stereoisomer (*R*)-1,4-dichloro-6-methylheptane (*S*)-cylcobut-2-en-1-ol

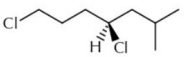
step 1: draw the connectivity



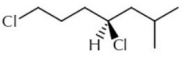
1,4-dichloro-6-methylheptane

cylcobut-2-en-1-ol

step 2: add 3D where needed
draw the geometry that is easy to assign



step 3: assign the geometrical label
you either drew the right one, or you have made the other one

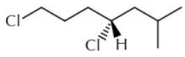


(*S*)-1,4-dichloro-6-methylheptane

(*S*)-cylcobut-2-en-1-ol

the one drawn is (*S*)-, so done

the one drawn is (*S*)-, so using the property of stereogenic atoms, swap the "H" and the "C" and make the (*R*)-



(*R*)-1,4-dichloro-6-methylheptane

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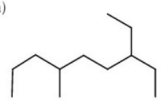
PRACTICE QUESTIONS

5.08 Each of the following connectivities either has one source of stereoisomerism or it has none.

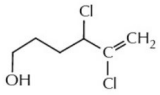
For those with one source, draw 3D representations (lines, dash, and wedge notation) for the two resulting stereoisomers and provide the appropriate stereochemical labels (*R/S*, *E/Z*, *cis/trans*).

For those with no source of stereoisomerism, invent a structural isomer of that molecule that has one (and only one) source of stereoisomerism, then draw and label both stereoisomers as above. *This is a great question to use for comparing and checking possible answers with your peers.*

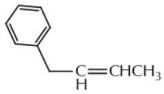
(a)



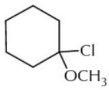
(b)



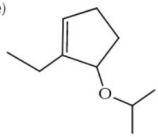
(c)



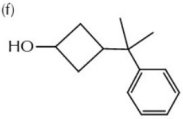
(d)



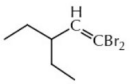
(e)



(f)



(g)



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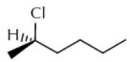
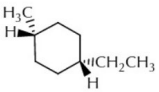
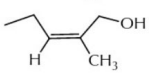
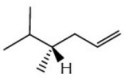
5.09 Provide complete IUPAC names for the following molecules, including the label for the stereochemical configuration.

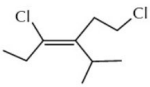
(a) 

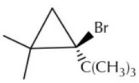
(b) 

(c) 

(d) 

(e)

(f) 

(g) 

5.10 Draw the following molecules, including a clear indication of the 3D structure indicated by the stereochemical label.

(a) (*E*)-1,5,5-tribromo-4-ethylhept-3-ene

(b) (*cis*)-4-phenylcyclohexan-1-ol

(c) (*R*)-4-chlorohept-1-ene

(d) (*S*)-1,1,2,2,3-pentafluorocyclopentane

(e) (*trans*)-1,5-diisobutylcyclooctane

(f) (*Z*)-3-bromo-2-chloro-1,1,1-trifluorohex-2-ene

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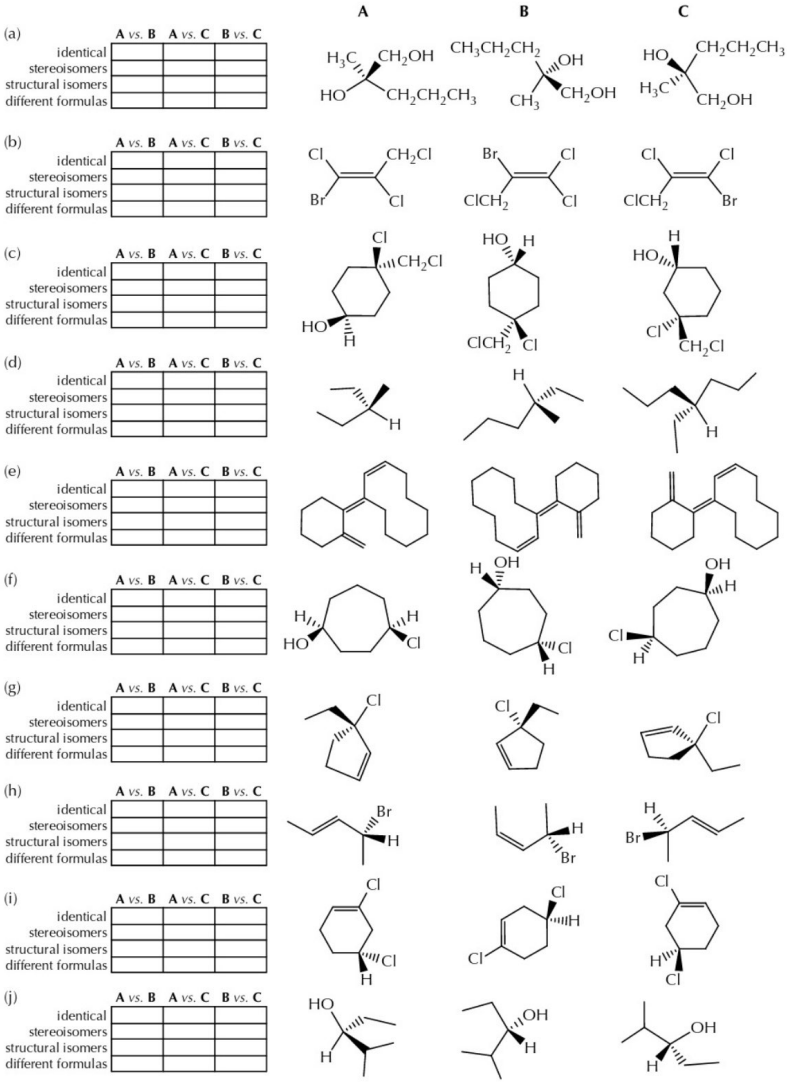
5.11 For each of the following trios of structures (**A**, **B**, and **C**), there are three binary comparisons you can make (**A** *versus* **B**, **A** *versus* **C**, and **B** *versus* **C**). For each comparison, tell whether the indicated pair are identical molecules, stereoisomers, structural isomers, or molecules with different molecular formulas.



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5.3 Chirality and Optical Activity in Molecules with a Single Source of Stereoisomerism

A. Detecting and Defining Handedness in the Macroscopic and Nanoscopic Worlds

In the world, there are many objects that are described as being handed—a specific reference to things that you interact with or operate differently depending on whether your right or left hand is being used. All sorts of spirals have their sense of twist defined as being right or left handed, such as springs, nuts, bolts, screw caps, and even spiral staircases. Other common right- and left-handed objects that you might have encountered include scissors, gloves, shoes, golf clubs, and student desks. And perhaps, obviously, your own hands and feet are "handed" also.

One of the defining qualities of handed objects is that there are two (and only two) versions: the one we call left and the other we call right. Although the historical term for such an object is "handed," a new term was invented for molecules that show handedness: chiral (ancient Greek for "hand"). The word "chiral" (pronounced with a hard "k" sound, as in the Greek letter chi) is now used generically to refer to any handed system. A spiral staircase is a chiral object. Your hands are both chiral. A commonly used form of the word is chirality, so some questions might be "what is the origin of the chirality in that object?" or "is that a chiral object?"

The operational definition of a chiral, or handed, system is one that produces a pair of nonidentical mirror image objects. It is recognized that, while different, the right- and left-handed versions of anything do have a relationship: They are nonidentical reflections of one another. Hold your two hands up in front of you, open palm to open palm, separated by a few inches. It is as though your two hands were reflecting one another in an imaginary mirror that was placed between them. Put a pair of shoes or a pair of gloves side by side and you can see the same effect. The objects are nonidentical (they cannot be superimposed on one another) but they have this mirror image relationship, and so they are deemed to be chiral (i.e., handed) objects (Figure 0530 on next page).

As mentioned in the introductory essay to this chapter, naturally occurring quartz crystals are chiral, as they occur naturally in either a right-handed or left-handed solid form. In 1885, the term "enantiomorph" was invented to classify these nonidentical mirror image two crystal forms; the word means "in opposite shape." Other than the obvious and observable difference in their crystalline forms, the left- and right-handed forms of quartz had absolutely identical properties.

In the early 1800s, the first polarizing filters for light were created. In general, these are materials that can absorb light that is oriented along one direction (e.g., horizontal) and lets the light in the other orientation (e.g., vertical) get through. The various Polaroid materials, first invented in the early 1900s, are used in sunglasses for this reason. Reflected glare is mostly horizontal, and so the orientation of the microcrystals embedded in the lenses is also lined up horizontally so that the light from reflected glare is absorbed. And when light, which is naturally propagating in all directions, passed through a polarizing filter, it ends up being linearly oriented (vertically in the case of sunglasses) and called linearly-polarized or plane-polarized light. You can do this demonstration easily: Two Polaroid lenses held perpendicularly over one another effectively block all light from getting through. Some computer, mobile device, and automobile displays use LEDs that project polarized light, which can create a problem because, at the right angle, the information is blocked from view by polarizing lenses.

In 1811, the first observations of passing plane-polarized light through cut pieces of the quartz enantiomorphs was reported, and the properties of the left- and right-handed forms were unexpectedly different in this experiment. One "hand" of the quartz caused the plane of polarization of the light to turn to a

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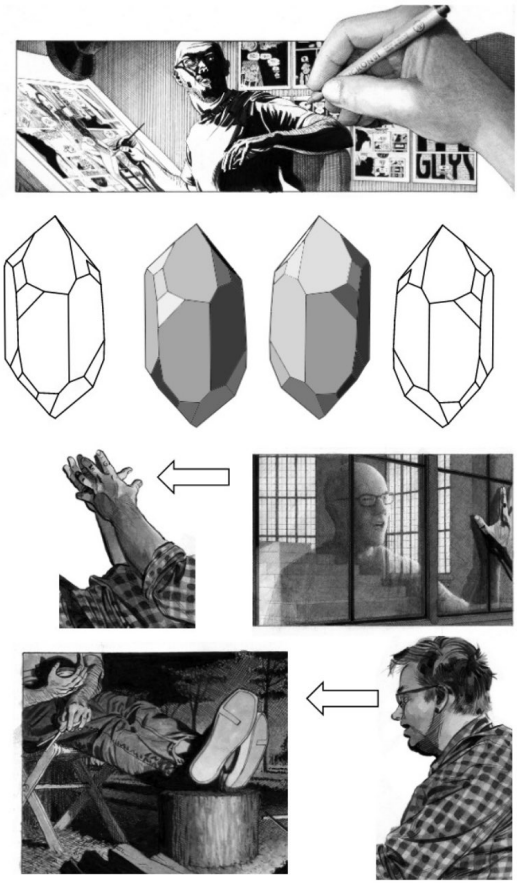
Figure 0530

Handedness (chirality).



Handedness (chirality) is defined by the human experience with pairs of three-dimensional objects with non-identical, mirror image relationship. One of the objects is the left-handed partner and the other is the right-handed partner. Our hands and feet are handed: hold your hands out in front of you, and they cannot superimpose on each other; instead, held out palm to palm, one hand looks as though it is the mirror reflection of the other. Most people have a dominant hand for writing and drawing, and a dominant foot for kicking. The clothing for our handed body parts needs to be handed. Some of the tools we use with our hands are handed: scissors, jar lids, golf clubs, nuts and bolts. We describe naturally occurring objects with this property as handed, such as in right- and left-handed quartz crystals, DNA, weather patterns, and galaxies.

different angle coming out of the crystal compared to when it entered, and the other hand had an equal but opposite effect (Figure 0531). If one of them turned the plane of polarization by +27° (called dextrorotatory, to turn to the right) then an equivalent sample of the other one turned the plane of polarization by -27° (called levorotatory, to turn to the left). At a given thickness, and at a specified temperature, and using a standard light source, this angle or rotation is a reproducible property, and it was called the specific rotation of the crystalline form. The general name of this property, where enantiomorphic crystal forms had an equal and opposite effect on plane-polarized light, was called optical activity. Chiral crystalline materials, such as quartz, are optically active. Materials that did not exhibit this property were called optically inactive and achiral ("not chiral"). The instrument used to measure optical activity is called a polarimeter.

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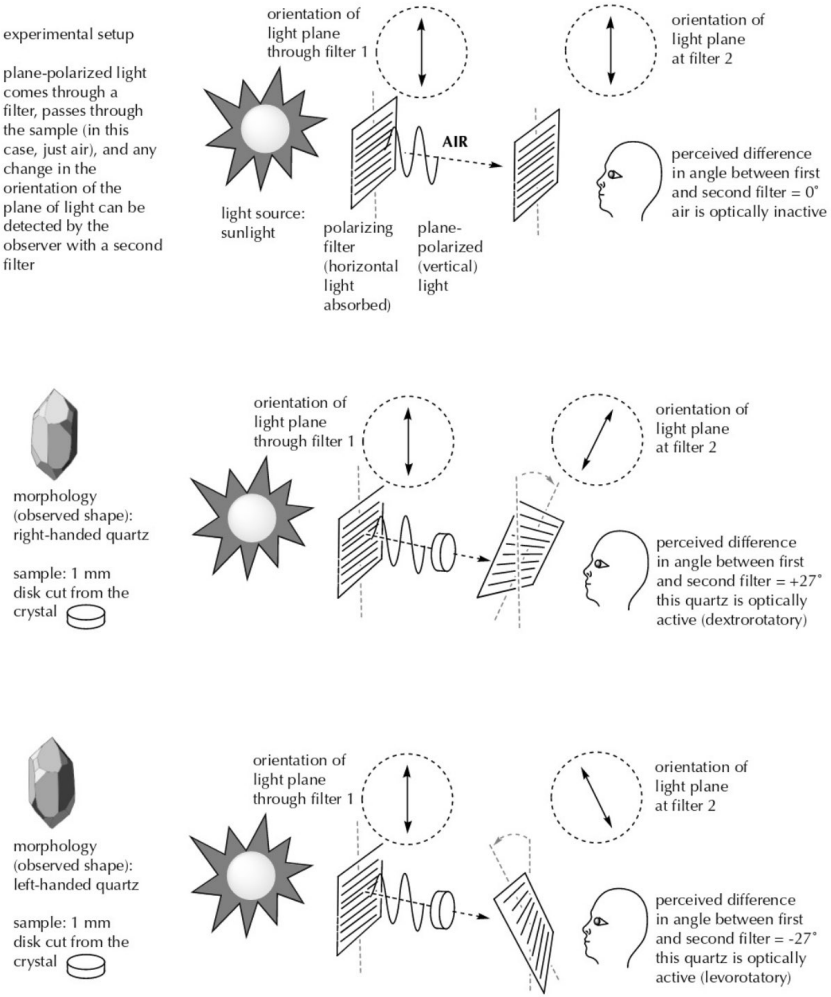
Figure 0531

Enantiomorphic forms of quartz and their optical activity.


experimental setup
plane-polarized light comes through a filter, passes through the sample (in this case, just air), and any change in the orientation of the plane of light can be detected by the observer with a second filter
orientation of light plane through filter 1
orientation of light plane at filter 2
AIR
light source: sunlight
polarizing filter (horizontal light absorbed)
plane-polarized (vertical) light
perceived difference in angle between first and second filter = 0°
air is optically inactive
morphology (observed shape): right-handed quartz
sample: 1 mm disk cut from the crystal
orientation of light plane through filter 1
orientation of light plane at filter 2
perceived difference in angle between first and second filter = +27°
this quartz is optically active (dextrorotatory)
morphology (observed shape): left-handed quartz
sample: 1 mm disk cut from the crystal
orientation of light plane through filter 1
orientation of light plane at filter 2
perceived difference in angle between first and second filter = -27°
this quartz is optically active (levorotatory)

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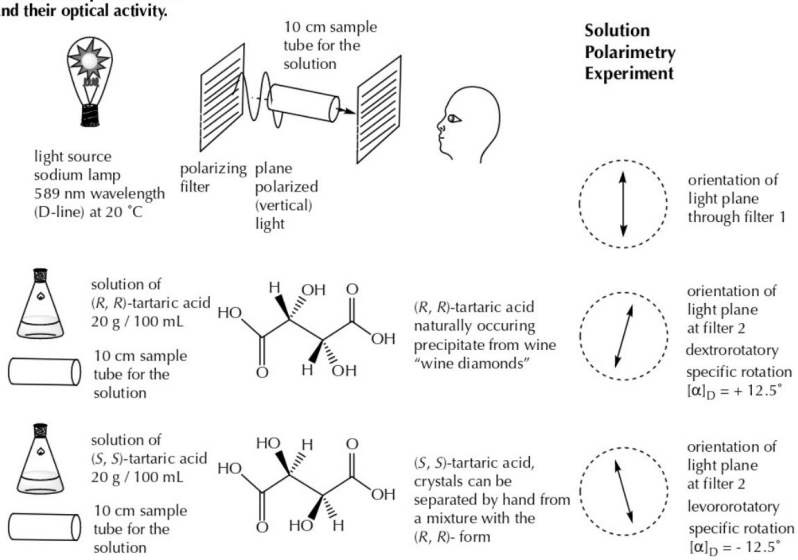
Within a few years, organic materials were tested, and some were observed to be optically active while others were not. Louis Pasteur, in 1848, deduced that optical activity was a molecular property, having physically separated mirror image crystals of tartaric acid, an organic compound that occurred in naturally enantiomorphic forms, and demonstrating that solutions of these substances were optically active—observable even after the destruction of the crystal forms had taken place when the substances dissolved (Figure 0532). As with the quartz crystals, the optical activity effect (called the specific rotation, $[\alpha]_D$) was equal and opposite for comparably prepared solutions of the mirror image crystals of tartaric acid. Although there was no model to explain these molecular differences, such pairs of substances were called optical isomers.

Figure 0532

Solutions of optical isomers and their optical activity.


10 cm sample tube for the solution
Solution Polarimetry Experiment
light source sodium lamp 589 nm wavelength (D-line) at 20 °C
polarizing filter
plane polarized (vertical) light
orientation of light plane through filter 1
solution of (R, R)-tartaric acid 20 g / 100 mL
10 cm sample tube for the solution
(R, R)-tartaric acid naturally occuring precipitate from wine "wine diamonds"
orientation of light plane at filter 2
dextrorotatory
specific rotation [α]D = + 12.5°
solution of (S, S)-tartaric acid 20 g / 100 mL
10 cm sample tube for the solution
(S, S)-tartaric acid, crystals can be separated by hand from a mixture with the (R, R)- form
orientation of light plane at filter 2
levororotatory
specific rotation [α]D = - 12.5°

Experimentally, the absolute value of an observed rotation angle (α_{OBS}) depends on several factors: (a) the concentration of the sample, (b) the solvent used, (c) the temperature, (d) the pathlength of the sample tube, and (e) the wavelength of the light used. The quantitative factors are incorporated as variables in the value of the specific rotation, and all of these experimental factors need to be reported as part of the experiment.

specific rotation $[\alpha]_{\lambda}^{\Theta} = (\alpha_{OBS})/(l \times c)$
λ = wavelength; Θ = temperature (°C); l = pathlength (dm); c = concentration (g/mL) in a solvent

A typical report: (*S*)-2-bromobutane has a specific rotation $[\alpha]_D^{20} = +23.1$ (*c* 1.00, ethanol)

The standard instrument uses a 1 dm sample tube, and "D" stands for the "D-line" (589 nm wavelength) of a sodium vapor lamp.

In 1874, as described in this chapter's introductory essay, chemists van't Hoff and Le Bel made the leap in thinking that optical isomerism could be explained by proposing that molecules themselves could have enantiomorphic, three-dimensional shapes. If, in the macroscopic world, the observable enantio-

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morphic crystalline forms of quartz were optically active, then, in the nanoscopic world of molecules, enantiomorphic forms might be the explanation.

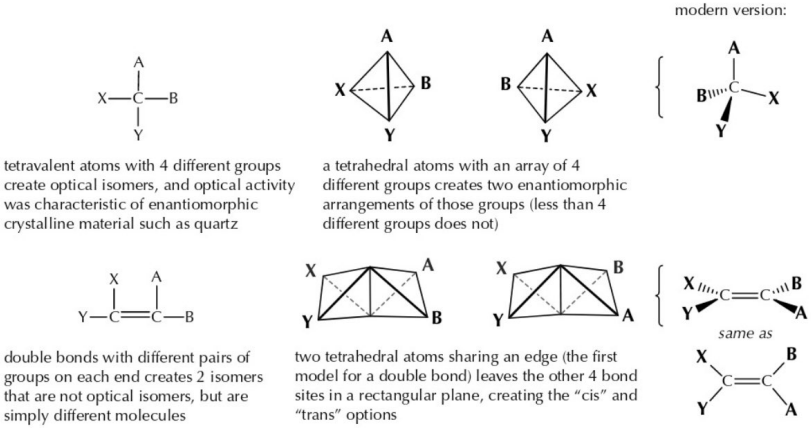
For van't Hoff and Le Bel, two problems in understanding isomerism were solved by thinking of atoms as being tetrahedral in shape: the optical isomers for tetravalent atoms and the geometrical isomers of some double bonds.

Optical isomers were explained because of the consistent observation that an atom with four different attached groups was a prerequisite for substances that were optically active. A tetrahedral array could produce two (and only two) arrangements that were enantiomorphs: nonidentical mirror images of one another (Figure 0533). As with their macroscopic counterparts, both enantiomorphic molecules are optically active, with opposite specific rotations, and considered to be chiral molecules.

Geometrical isomers. Interestingly enough, as Figure 0533 also shows, tetrahedral atoms also solved the problem of why some molecules with double bonds existed as a pair of isomers while others did not. By connecting two tetrahedral atoms along an edge, which was imagined to be a double bond, the remaining bonding sites were coplanar and could create two (and only two) arrangements: *cis* and *trans*. The *cis* and *trans* isomers of a double bond are not enantiomorphic in shape with respect to one another, they are nonenantiomorphic versions of different molecules with the same connectivity; both of the *cis* and *trans* isomers are optically inactive and considered to be achiral molecules. Although we understand the bonding of double bonds differently today, the tetrahedral atom model persisted through the 1940s, until ideas about sigma and pi bonding were accepted.

Figure 0533

Two isomerism problems were solved by using tetrahedral atoms (1874).



tetravalent atoms with 4 different groups create optical isomers, and optical activity was characteristic of enantiomorphic crystalline material such as quartz

a tetrahedral atoms with an array of 4 different groups creates two enantiomorphic arrangements of those groups (less than 4 different groups does not)

double bonds with different pairs of groups on each end creates 2 isomers that are not optical isomers, but are simply different molecules

two tetrahedral atoms sharing an edge (the first model for a double bond) leaves the other 4 bond sites in a rectangular plane, creating the "cis" and "trans" options

Although controversial in 1874, within 20 years the general idea of explaining these forms of isomerism with three-dimensional atoms was widely accepted. The words stereochemistry (1890) and stereoisomer (1894) arise in this era as classifications.

In 1929, a pair of stereoisomers with enantiomorphic structures was further classified as a pair of "enantiomers" (meaning: in opposite parts). Each member of a pair of enantiomers is chiral and optically active with equal and opposite specific rotations (e.g., the *R*-isomer versus the *S*-isomer). And in 1936, the generic

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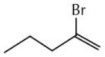
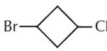
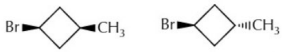
term "diastereomer" (meaning: not comparable) was invented for any pair of stereoisomers that were not enantiomers (e.g., the *cis*-isomer versus the *trans*-isomer). Nothing can be said about the properties of a pair of diastereomers except that their properties will be different (not comparable). See Figure 0534 for a summary review about isomerism.

Figure 0534

Overview of molecular structural isomerism and its terminology.

C_5H_9Br

Same molecular formula, different connectivity = structural (constitutional) isomers	Source of stereoisomerism?	Same connectivity, different geometry = stereoisomers
 2-bromo-1-pentene	none	none, single unique molecule of the 2-bromo-1-pentene connectivity optically inactive
 1-bromo-3-methylcyclobutane	a symmetrical ring with an even number of atoms and substituted at opposite vertices	 *cis*-1-bromo-3-methylcyclobutane; *trans*-1-bromo-3 methylcyclobutane; diastereomers (both are achiral, optically inactive)
4-bromo-1-pentene	a tetrahedral atom with four different substituent groups	(*R*)-4-bromo-1-pentene; (*S*)-4-bromo-1-pentene; enantiomers (both are chiral, optically active)
$CH_3CH_2CH_2CH{=}CHBr$ 1-bromo-1-pentene	a double bond that is unsymmetrically substituted at both ends	(*E*)-1-bromo-1-pentene; (*Z*)-1-bromo-1-pentene; diastereomers (both are achiral, optically inactive)

B. Tetrahedral Atoms with Four Different Substituents

Now we bring together the single structural sources of stereoisomers from Section 5.2 together with the properties described in Section 5.3A, starting with molecules with a single stereocenter, that is, a tetrahedral atom with four different substituent groups.

Because stereochemistry is a property of molecular structure and not of chemical reactivity, there is no variation to the analysis based on the identity of the atoms. The stereochemical analysis of every molecule possessing a single tetrahedral stereocenter is exactly the same, and that means that the classification (diagnosis) process is once again critical to understanding how to apply these ideas.

The Bottom Line: For molecules with one tetrahedral stereocenter as a source of stereoisomerism, there are two (and only two) stereoisomers. One of them will carry the geometrical label "R" and the other will be the "S" geometry. The stereoisomeric tetrahedral "R" and "S" geometries are nonidentical mirror images, so this pair of stereoisomers has the enantiomer relationship. Both are chiral. Both are optically active. It is not possible to predict either the magnitude or direction of the specific rotation, except to say that when you determine one of them (e.g., one of them has a specific rotation of +4.5°) then the enantiomer will be

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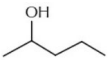
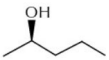
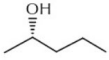
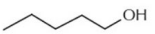
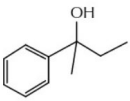
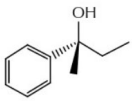
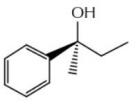
exactly the opposite (-4.5°). There is no predictive relationship whatsoever between the artificial label ("R" and "S") and the measured property of the specific rotation, other than this fact of equal and opposite values. Figure 0535 summarizes these ideas with examples that both fit and do not fit this classification.

Figure 0535

Examples that include analyses for molecules with one tetrahedral stereocenter.

connectivity	source of stereoisomerism	stereoisomers	
 2-pentanol	a tetrahedral atom with four different substituent groups	 (*R*)-2-pentanol $[a]_D$ -13° (neat) mp -50 °C bp 118-119 °C	 (*S*)-2-pentanol $[a]_D$ +13° (neat) mp -50 °C bp 118-119 °C
cyclohex-2-en-1-ol	a tetrahedral atom with four different substituent groups	(*S*)-cyclohex-2-en-1-ol $[a]_D$ -117-120° 5 g/100 mL $CHCl_3$ mp 107-108 °C bp 164-166 °C	(*R*)-cyclohex-2-en-1-ol $[a]_D$ +117-120° 1.5 g/100 mL $CHCl_3$ mp 107-108 °C bp 164-166 °C
1-cyclohexanol	none	none, single unique molecule of the 1-cyclohexanol connectivity mp 26 °C bp 162 °C	
2-bromo-3-methylbutane	a tetrahedral atom with four different substituent groups	(*S*)-2-bromo-3-methylbutane $[a]_D$ +2.56° (neat) mp -105 °C (est) bp 123 °C	(*R*)-2-bromo-3-methylbutane $[a]_D$ -2.56° (neat) mp -105 °C (est) bp 123 °C
 1-pentanol	none	none, single unique molecule of the 1-pentanol connectivity mp -78 °C bp 137-139 °C	
 2-phenyl-2-butanol	a tetrahedral atom with four different substituent groups	 (*R*)-2-phenyl-2-butanol $[a]_D$ +17.5° (neat) mp unreported bp 246 °C	 (*S*)-2-phenyl-2-butanol $[a]_D$ -17.5° (neat) mp unreported bp 246 °C

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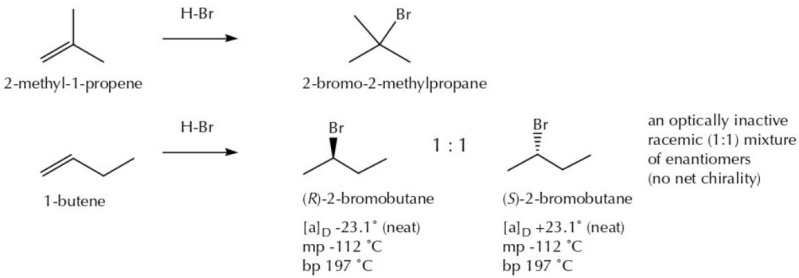
Stereochemical analysis is a critical part of real-world organic chemistry. Many, if not most, biologically active compounds used as medicines, for example, are chiral (nature only produces either the right-hand or left-hand version). Your body is also inherently chiral because the molecular catalysts used to carry out reactions (enzymes) are also chiral molecules. As a result, your body (to use a simple comparison) is filled with enzymes that are like empty left- and right-handed gloves. A molecule you consume that is a left-hand match will be properly acted upon by a left-handed enzyme (the hand fits the glove) and the right-hand version of the molecule is likely to be invisible to this enzyme. This statement does not mean that the right-hand version is ignored, because there might be another enzyme, somewhere else, that would do something else.

The general principle in those examples is that the only way to discriminate between a pair of chiral objects is to act upon them in a chiral environment, otherwise their properties are the same. Individually, two enantiomers have the same boiling points, same melting points, same solubilities, same NMR spectra, and so on, because all of these environments are achiral. On the other hand, they may have different odors, different tastes, and be metabolized differently in the body, because your human systems are inherently chiral.

When you carry out a chemical reaction, this same principle holds, too. If you start with no net chirality, and you perform the operation in an achiral environment, then there can be no net chirality in the end. Figure 0536 provides two important examples of this. When you carry out the electrophilic addition reaction of HBr with 2-methyl-2-propene, neither the HBr nor the 2-methyl-2-propene are chiral. The major regioisomer, 2-bromo-2-methylpropane has no stereocenter or other source of stereoisomerism, and so it is achiral, and the principle holds.

Figure 0536

Examples of reactions that begin and end with no net chirality.



When the addition reaction is carried out on the isomeric alkene 1-butene, however, the story is a little different. As in the first example, HBr and 1-butene are both achiral. But now, the addition reaction creates 2-bromobutane, which has a stereocenter in it. Because the reaction cannot produce any net chirality, the only way to get an achiral product that also includes stereocenters is to produce an achiral mixture. And because the (*R*)-2-bromobutane and (*S*)-2-bromobutane have exactly the same properties in an achiral environment, they are formed at the same rate and end up in exactly equal amounts. The product, which is a 1:1 mixture of (*R*)-2-bromobutane and (*S*)-2-bromobutane, is considered to be an achiral mixture. Because the specific rotations of these two enantiomers are equal and opposite, a 1:1 mixture of these two will be optically inactive (net rotation of 0°). An optically inactive 1:1 mixture of enantiomers is called a racemic mixture. Another way to express this idea is to say that the addition of HBr to 1-butene shows

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no stereoselectivity, that is, of the possible stereoisomeric outcomes, one enantiomer of the product is not formed to the preference of the other.

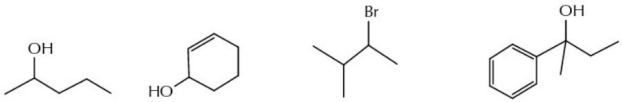
There are many new relationships to keep track of here. One useful exercise is to interrogate a molecule with a series of questions. Once you have classified it according to its stereochemical case, the answers to the questions are fixed and irrespective of the particular example. Figure 0537 gives a first example of such an interrogation, having already concluded that the molecule has a single (chiral) stereocenter as its source of stereoisomerism.

Figure 0537

Interrogation of a molecule with a single (chiral) stereocenter.

source of stereoisomerism

one tetrahedral atom with four different substituent groups



2-pentanol | cyclohex-2-en-1-ol | 2-bromo-3-methylbutane | 2-phenyl-2-butanol

Question:	Answer:
How many stereoisomers are represented by this connectivity?	two
What are the geometrical labels for the two stereoisomers?	(*R*) and (*S*)
Optically active: (*R*) only, (*S*) only, both, or neither?	both
How many optically active enantiomers does the (*R*) isomer have?	one [the (*S*) isomer]
If the solubility of the (*R*) isomer in water is 0.5 g/mL, what about (*S*)?	0.5 g/mL
How many diastereomers does the (*R*) isomer have?	none
Chiral: (*R*) only, (*S*) only, both, or neither?	both
Is a 1:2 mixture of (*R*) to (*S*) optically active or inactive?	optically active
Is the (*R*) stereoisomer dextrorotatory (+) or levorotatory (-)?	cannot predict, experimentally determined
If the (*S*) stereoisomer has a specific rotation of +67°, what about (*R*)?	-67°
If the (*S*) stereoisomer has a boiling point of 114 °C, what about (*R*)?	114 °C

C. Double Bonds That Are Unsymmetrically Substituted at Both Ends

The Bottom Line: For molecules with one double bond, unsymmetrically substituted at both ends, as a source of stereoisomerism, there are two (and only two) stereoisomers. One of them will carry the geometrical label "E" and the other will be the "Z" geometry. The stereoisomeric "E" and "Z" geometries are not mirror images, so they are not enantiomers; this pair of stereoisomers has the diastereomer (stereoisomers that are not enantiomers) relationship. Both are achiral. Both are optically inactive. Their various physical and chemical properties are expected to be altogether different. Figure 0538 on the next page summarizes these ideas with examples that both fit and do not fit this classification.

Returning for a moment to the term "diastereomer." Its usage is in direct contrast with "enantiomer" in many respects. While the term enantiomer refers to a quite specific relationship between two molecules identified as stereoisomers (nonidentical mirror images; in your experience so far, one being "R" and the other being "S"), the term diastereomer is a negatively defined relationship between a pair of stereoisomers because the best operational definition for the term "diastereomer" is "a pair of stereoisomers that are not enantiomers." Both parts of that last phrase are important.

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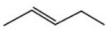
Figure 0538

Examples that include analyses for molecules with one double bond, unsymmetrically substituted at both ends.

connectivity	source of stereoisomerism	stereoisomers	
$CH_3CH{=}CHCH_2CH_3$ 2-pentene	a double bond that is unsymmetrically substituted at both ends	 (*E*)-2-pentene optically inactive mp -140 °C bp 36 °C dipole moment 0.00 D	 (*Z*)-2-pentene optically inactive mp -151 °C bp 37 °C dipole moment 0.30 D
 1-chlorocyclohex-1-ene	a double bond that is unsymmetrically substituted at both ends	 1-chlorocyclohex-1-ene optically inactive mp unreported bp 143 °C dipole moment 1.69 D	no other observable stereoisomers because the 6-membered ring is too small; a single unique molecule of 1-chlorocyclohex-1-ene connectivity
$CH_3CH{=}CHCl$ 1-chloro-1-propene	a double bond that is unsymmetrically substituted at both ends	 (*E*)-1-chloro-1-propene optically inactive mp -99 °C bp 36 °C dipole moment 1.97 D	 (*Z*)-1-chloro-1-propene optically inactive mp -135 °C bp 35 °C dipole moment 1.67 D
 1-pentene	none	 none, single unique molecule of the 1-pentene connectivity optically inactive mp -165 °C bp 30 °C dipole moment 0.48 D	

The comparison is between two molecules already deemed to be stereoisomers. Figure 0539 gives another example of an interrogation, this time for a double bond for which stereoisomers are possible.

D. Symmetrical Rings with an Even Number of Atoms and Substituted at Opposite Vertices

The Bottom Line: For molecules with symmetrical rings containing an even number of atoms and substituted at opposite vertices as a source of stereoisomerism, there are two (and only two) stereoisomers. Both are achiral. Both are optically inactive. Their various physical and chemical properties are expected to be altogether different. When a pair of hydrogen atoms is being compared (one at each of the opposite vertices) the geometrical labels "cis" and "trans" can be used to name them. A more complex system (see Appendix 3) is used to name other cases. These stereoisomers are not mirror images, so they are diastereomers. Figure 0540 summarizes these ideas with examples that both fit and do not fit this classification. Figure 0541 gives another example interrogating a molecule in this classification.

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Figure 0539

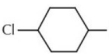
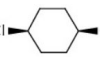
Interrogation of a molecule with a double bond capable of stereoisomerism.

source of stereoisomerism	$CH_3CH{=}CHCH_2CH_3$	$ClCH{=}CHCH_3$	$CH_3(Br)C{=}C(Br)CH_2CH_2OH$
a double bond that is unsymmetrically substituted at both ends	2-pentene	1-chloro-1-propene	3,4-dibromopent-3-en-1-ol

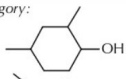
Question:	Answer:
How many stereoisomers are represented by this connectivity?	two
What are the geometrical labels for the two stereoisomers?	(*E*) and (*Z*)
Optically active: (*E*) only, (*Z*) only, both, or neither?	neither
How many optically active enantiomers does the (*E*) isomer have?	none
If the solubility of the (*E*) isomer in ethanol is 0.1 g/mL, what about (*Z*)?	cannot predict, experimentally determined
How many diastereomers does the (*Z*) isomer have?	one
Chiral: (*E*) only, (*Z*) only, both, or neither?	neither
Is a 1:2 mixture of (*E*) to (*Z*) optically active or inactive?	optically inactive in any proportion
Is the (*E*) stereoisomer dextrorotatory (+) or levorotatory (-)?	neither, it is optically inactive
How many enantiomers does the (*E*) isomer have?	none
If the (*E*) stereoisomer has a boiling point of 114 °C, what about (*Z*)?	cannot predict, experimentally determined

Figure 0540

Examples that include analyses for molecules with symmetrical rings containing an even number of atoms and substituted at opposite vertices.

connectivity	source of stereoisomerism	stereoisomers	
1,3-dimethylcyclobutane	a symmetrical ring with an even number of atoms and substituted at opposite vertices	(*cis*)-1,3-dimethylcyclobutane optically inactive bp 61 °C dipole moment 0.17 D	(*trans*)-1,3-dimethylcyclobutane optically inactive bp 58 °C dipole moment 0.13 D
4-methylcyclohexan-1-ol	a symmetrical ring with an even number of atoms and substituted at opposite vertices	(*trans*)-4-methylcyclohexan-1-ol optically inactive bp 173-175 °C mp unreported dipole moment 1.90 D	(*cis*)-4-methylcyclohexan-1-ol optically inactive bp 171-172 °C mp -9 °C dipole moment 1.75 D
 1,4-dichlorocyclohexane	a symmetrical ring with an even number of atoms and substituted at opposite vertices	(*trans*)-1,4-dichlorocyclohexane optically inactive mp 101 °C dipole moment 0.00 D	 (*cis*)-1,4-dichlorocyclohexane optically inactive mp 18 °C dipole moment 2.89 D

neither of these is within this category:

2,4-dimethylcyclohexan-1-ol 

1,2-dimethylcyclopentane

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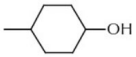
Figure 0541

Interrogation of a molecule with symmetrical rings containing an even number of atoms and substituted at opposite vertices.

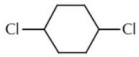
source of stereoisomerism

a symmetrical ring with an even number of atoms and substituted at opposite vertices

1,3-dimethylcyclobutane



4-methylcyclohexan-1-ol



1,4-dichlorocyclohexane

Question:	Answer:
How many stereoisomers are represented by this connectivity?	two
What are the geometrical labels for the two stereoisomers?	(*cis*) and (*trans*)
Optically active: (*cis*) only, (*trans*) only, both, or neither?	neither
How many optically active enantiomers does the (*cis*) isomer have?	none
If the solubility of the (*cis*) isomer in hexane is 2 g/mL, what about (*trans*)?	cannot predict, experimentally determined
How many diastereomers does the (*trans*) isomer have?	one
Chiral: (*cis*) only, (*trans*) only, both, or neither?	neither
Is a 1:2 mixture of (*cis*) to (*trans*) optically active or inactive?	optically inactive in any proportion
Is the (*trans*) stereoisomer dextrorotatory (+) or levorotatory (-)?	neither, it is optically inactive
How many enantiomers does the (*cis*) isomer have?	none
If the (*trans*) stereoisomer has a boiling point of 114 °C, what about (*cis*)?	cannot predict, experimentally determined

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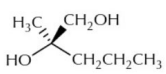
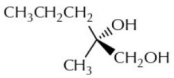
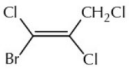
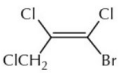
PRACTICE QUESTIONS

5.12 For each of the following pairs of structures (**A** and **B**), tell whether the molecules are identical structures, stereoisomers, structural isomers, or molecules with different molecular formulas. In every case, indicate the stereoisomeric relationship (enantiomer, diastereomer, not applicable) and which of the molecules is expected to be optically active.

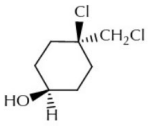
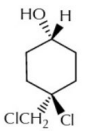
	A	B	enantiomers	diastereomers	not applicable	optically active
(a) identical						
stereoisomers						
structural isomers						
different formulas						

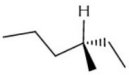
	A	B	enantiomers	diastereomers	not applicable	optically active
(b) identical						
stereoisomers						
structural isomers						
different formulas						

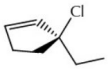
	A	B	enantiomers	diastereomers	not applicable	optically active
(c) identical						
stereoisomers						
structural isomers						
different formulas						

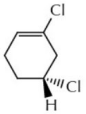
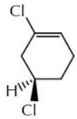
	A	B	enantiomers	diastereomers	not applicable	optically active
(d) identical						
stereoisomers						
structural isomers						
different formulas						



	A	B	enantiomers	diastereomers	not applicable	optically active
(e) identical						
stereoisomers						
structural isomers						
different formulas						



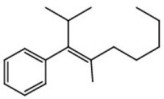
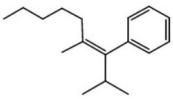
	A	B	enantiomers	diastereomers	not applicable	optically active
(f) identical						
stereoisomers						
structural isomers						
different formulas						

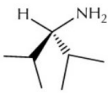
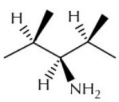
	A	B	enantiomers	diastereomers	not applicable	optically active
(g) identical						
stereoisomers						
structural isomers						
different formulas						

	A	B	enantiomers	diastereomers	not applicable	optically active
(h) identical						
stereoisomers						
structural isomers						
different formulas						

	A	B	enantiomers	diastereomers	not applicable	optically active
(i) identical						
stereoisomers						
structural isomers						
different formulas						

	A	B	enantiomers	diastereomers	not applicable	optically active
(j) identical						
stereoisomers						
structural isomers						
different formulas						

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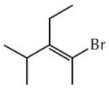
5.13 Answer the questions associated with this particular structure.



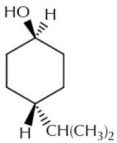
(a) What is the complete IUPAC name for this compound?

(b) Is this molecule optically active? Why or why not?

(c) How many other stereoisomers are there for this connectivity? Explain.

(d) How many achiral diastereomers does this molecule have? Explain.

5.14 Answer the questions associated with this particular structure.



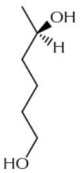
(a) What is the complete IUPAC name for this compound?

(b) Is this molecule optically active? Why or why not?

(c) How many other stereoisomers are there for this connectivity? Explain.

(d) How many chiral diastereomers does this molecule have? Explain.

5.15 Answer the questions associated with this particular structure.



(a) What is the complete IUPAC name for this compound?

(b) Is this molecule optically active? Why or why not?

(c) How many other stereoisomers are there for this connectivity? Explain.

(d) How many diastereomers (chiral and achiral) does this molecule have? Explain.

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5.16 Answer the questions associated with this particular structure.

$[\alpha]_D = -158°$
0.012 g/100 mL
in benzene

bp 72 °C
mp -127 °C

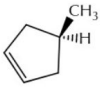
(a) What is the complete IUPAC name for the enantiomer of this compound?

(b) What is the specific rotation of the enantiomer of this compound?

(c) How many other stereoisomers are there for this connectivity? Explain.

(d) What is the boiling point of the enantiomer of this compound?

5.17 Answer the questions associated with this particular structure.



bp 75 °C
mp -161 °C

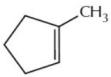
(a) What is the complete IUPAC name for this compound?

(b) What is the value of the specific rotation of this compound? Why?

(c) How many other stereoisomers are there for this connectivity? Explain.

(d) How many ^{13}C-NMR signals will this molecule have?

5.18 Answer the questions associated with this particular structure.



bp 76 °C
mp -142 °C

(a) What is the complete IUPAC name for this compound?

(b) Is this molecule optically active? Why or why not?

(c) How many other stereoisomers are there for this connectivity? Explain.

(d) How many ^{13}C-NMR signals will this molecule have?

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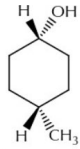
5.19 Answer the questions associated with this particular structure.



bp 172-173 °C
mp -10 °C
dm 1.75 D

(a) What is the complete IUPAC name for this compound?

(b) What is the specific rotation of this compound?

(c) This connectivity has another stereoisomer. What is its name and relationship to this one?

(d) What is the boiling point, melting point, and dipole moment of the other stereoisomer?

5.20 Answer the questions associated with this particular structure.

bp 178 °C
mp -38 °C
solubility in water
= 1.12 g/L
$[a]_D$ -10° (neat)

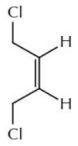
(a) What is the complete IUPAC name for this compound?

(b) Four properties are listed here. What are the values for the enantiomer of this compound?

(c) How many diastereomers are there for this connectivity? Explain.

(d) How many ^{13}C-NMR signals will this molecule have?

5.21 Answer the questions associated with this particular structure.



bp 152 °C
mp -48 °C
dm 1.19 D

(a) What is the complete IUPAC name for this compound?

(b) Is this molecule optically active? Why or why not?

(c) Three properties are listed here. What are the values for the diastereomer of this compound?

(d) How many ^{13}C-NMR signals will this molecule have? How about its diastereomer?

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5.4 Chirality and Optical Activity in Molecules with Multiple Sources of Stereoisomerism

A. Molecules with More Than One Chiral Stereocenter (Unsymmetrical, Dissimilar Centers)

This classification or case-based stereochemical analyses readily extends to molecules with more than one source of stereoisomerism. As stated previously, once you have classified a molecule correctly, its stereochemical analysis is a fixed answer that applies to every molecule in that classification.

In molecules where there are two chiral, tetrahedral stereocenters, the stereocenters will either be

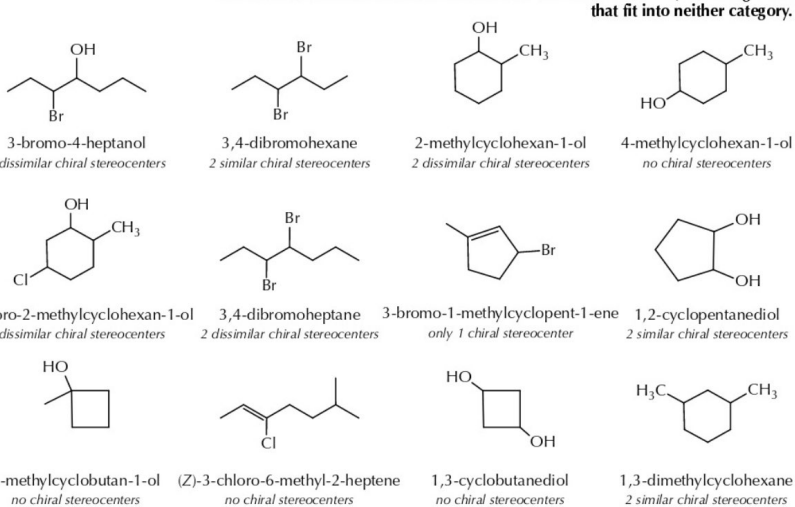
similar: two different chiral stereocenters, but each made up of the same four substituents; or

dissimilar: two different chiral stereocenters, where at least one substituent is different in the comparison between them.

Because the analysis depends on your ability to correctly distinguish between these two cases, Figure 0542 contains examples of molecules that fit into one, the other, or neither of these categories.

Figure 0542

Molecules with two similar or two dissimilar chiral stereocenters, including those that fit into neither category.



A stereochemical analysis for any structure includes how many stereoisomers will form and what their properties and relationships will be. Starting with two dissimilar chiral stereocenters, the analysis relies on some quite familiar ideas from probability and statistics. If you have two dissimilar chiral stereocenters in a molecule, and they could each be either the "R" or "S" geometry, then there are four possible combinations. This analysis is the same as the outcomes from throwing two different coins (a penny and a nickel), where there are four outcomes: penny(heads)-nickel(heads), penny(tails)-nickel(heads), penny(heads)-nickel(tails), and penny(tails)-nickel(tails).

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The Bottom Line: For molecules with two dissimilar chiral stereocenters as a source of stereoisomerism, there are four possible stereoisomers. The four stereoisomers are "R,R", "R,S", "S,R" and "S,S"; they are all four chiral and all four optically active. Four objects have six pairwise relationships: the "R,R" and "S,S" relationship is enantiomer, as is the "R,S" and "S,R" relationship. The other four pairwise relationships in this set ("R,R" and "R,S"; "R,R" and "S,R"; "S,S" and "R,S"; "S,S" and "S,R") are diastereomer. As enantiomers, the "R,R"/"S,S" pair will have equal and opposite specific rotations, although the values must be determined experimentally. A 1:1 mixture of either enantiomeric pair will be an optically inactive racemic mixture. Being diastereomers means that, for example, "R,R" and "R,S" are stereoisomers of the original connectivity, but beyond that their various properties are expected to be altogether different. Figure 0543 summarizes these ideas with examples that both fit and do not fit this classification. Figure 0544 gives another example interrogating a molecule in this classification.

Figure 0543

Examples that include analyses for molecules with two dissimilar chiral stereocenters.

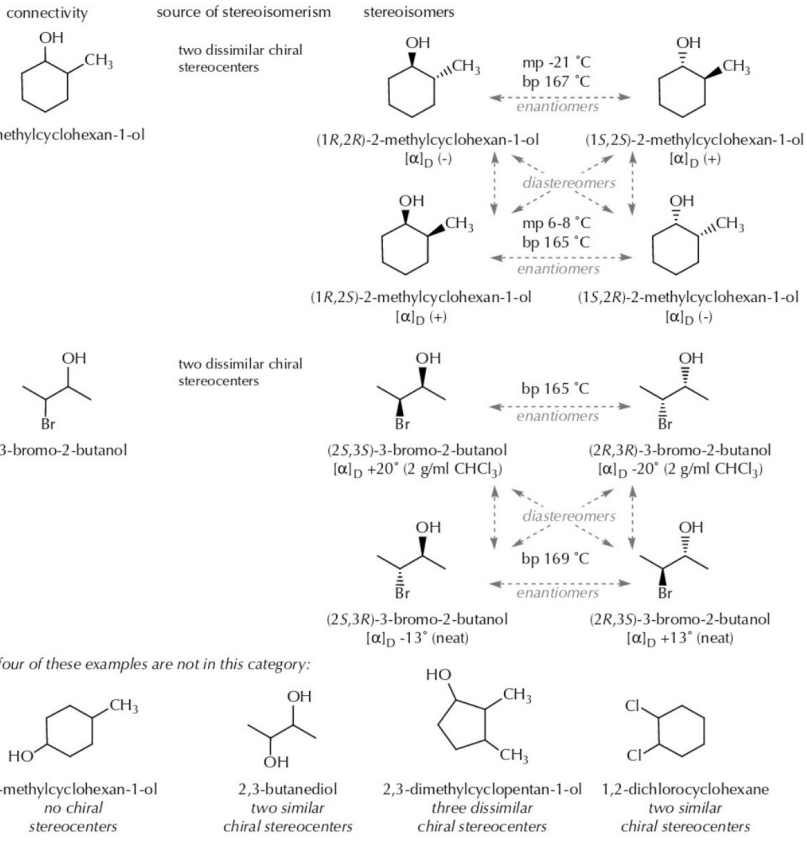

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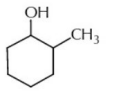
Figure 0544

Interrogation of a molecule with two dissimilar chiral stereocenters.

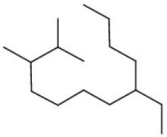
source of stereoisomerism

two dissimilar chiral stereocenters



2-methylcyclohexan-1-ol

3-bromo-2-butanol



8-ethyl-2,3-dimethyldodecane

Question:	Answer:
How many stereoisomers are represented by this connectivity?	four
What are the geometrical labels for the four stereoisomers?	(*R,R*)-, (*S,S*)-, (*R,S*)-, (*S,R*)-,
How many of the stereoisomers are optically active?	all 4 of them
How many optically active enantiomers does the (*R,R*)- isomer have?	one, the (*S,S*)-
If the solubility of the (*S,R*)- isomer in methanol is 1 g/mL, what about (*R,R*)-?	cannot predict, experimentally determined
How many optically active diastereomers does the (*S,S*)- isomer have?	two, the (*R,S*)- and (*S,R*)-
How many optically inactive diastereomers does the (*R,S*)- isomer have?	none
Is a 1:1 mixture of the (*S,S*)- and (*R,S*)- isomers optically active or inactive?	most likely active except by coincidence
Is the (*S,S*)- stereoisomer dextrorotatory (+) or levorotatory (-)?	cannot predict, experimentally determined
How many enantiomers does the (*R,S*)- isomer have?	one, the (*S,R*)- isomer
If the (*R,S*)- stereoisomer has a boiling point of 114 °C, what about (*S,R*)-?	114 °C
If the (*S,S*)- stereoisomer is dextrorotatory ([a]$_D$ +14°), what about (*R,R*)-?	$[\alpha]_D = -14°$
How many optically inactive diastereomers does the (*R,S*)- isomer have?	none
Is a 1:1 mixture of the (*S,S*)- and (*R,R*)- isomers optically active or inactive?	inactive (racemic mixture)

The stereochemical analysis for two dissimilar stereocenters extrapolates easily to molecules with greater than two. Without considering any specific structure at the moment, imagine a molecule with four dissimilar chiral stereocenters in it. Each chiral stereocenter could either be the "R" or "S" geometry, but now you are tossing four different coins, not two. Statistically, the number of outcomes from combining four binary choices is 2 x 2 x 2 x 2 or 16 possible outcomes. The probability mathematics is completely generalizable, so it is true that for "n" dissimilar stereocenters, the total number of possible stereoisomers is 2^n (4 dissimilar stereocenters -> 2^4 = 16 stereoisomers; this is called the Le Bel-van't Hoff Rule).

Following the interrogation strategy, there are many things that can be said about these 16 stereoisomers. An analysis for any molecule with four dissimilar chiral stereocenters is provided in Figure 0545, found on the following page. A specific molecule is shown in Figure 0546 (also on the next page), along with a variety of questions and how to apply the general analysis to give the answers.

Molecules with n dissimilar chiral stereocenters will have 2^n possible stereoisomers. All of the stereoisomers will be chiral. For any specific stereoisomer, it will have one (chiral) enantiomer and 2^n-2 (chiral) diastereomers. For example: For a molecule with 4 dissimilar stereocenters, one of the 16 stereoisomers is the "RRRR" compound. It has one enantiomer, the "SSSS" isomer. The other 14 stereoisomers all have the diastereomer relationship with the "RRRR" isomer and the "SSSS" isomer.

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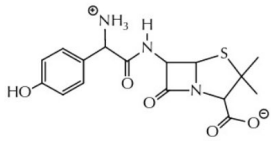
Figure 0545

Stereochemical analysis for every molecule with four dissimilar chiral stereocenters.

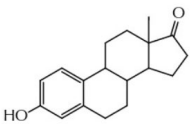
examples of connectivities

source of stereoisomerism

four dissimilar chiral stereocenters



amoxicillin
a common antibiotic



estrone
a female sex hormone

four dissimilar chiral stereocenters: each of them can be "R" or "S"

center 1	center 2	center 3	center 4
R S	R S	R S	R S

2 x 2 x 2 x 2 $= 2^4$ options = 16 combinations
= 16 stereoisomers

isomer number	center 1	center 2	center 3	center 4
1	R	R	R	R
3	S	R	R	R
5	R	S	R	R
7	R	R	S	R
2	S	S	S	S
4	R	S	S	S
6	S	R	S	S
8	S	S	R	S
9	R	R	R	S
11	S	S	R	R
13	S	R	S	R
15	S	R	R	S
10	S	S	S	R
12	R	R	S	S
14	R	S	R	S
16	R	S	S	R

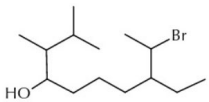
there are 8 pairwise enantiomer relationships: **1/2**; **3/4**; **5/6**; **7/8**; **9/10**; **11/12**; **13/14**; **15/16**
all other pairwise relationships are diastereomers: **1/3**; **1/4**; **1/5**... and so on

Figure 0546

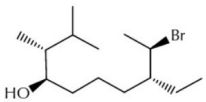
Interrogation of a molecule with four dissimilar chiral stereocenters.

source of stereoisomerism

four dissimilar chiral stereocenters



9-bromo-8-ethyl-2,3-dimethyldecan-4-ol



(3*R*,4*R*,8*R*,9*R*)-9-bromo-8-ethyl-2,3-dimethyldecan-4-ol

Question:

How many stereoisomers are represented by this connectivity?

The (*R*,*R*,*R*,*R*)- is shown; is it chiral?

How many of the 16 stereoisomers are optically active?

Answer:

sixteen

yes

all 16 of them

Interrogation continues on next page . . .

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Figure 0546 continued . . .

How many enantiomers does the (*R,R,R,R*)- isomer have?	one, the (*S,S,S,S*)-
Another stereoisomer is the (*R,S,R,R*)-; how many enantiomers does it have?	one, the (*S,R,S,S*)-
How many optically active diastereomers does the (*R,R,R,R*)- isomer have?	14
How many optically active diastereomers does the (*S,R,R,S*)- isomer have?	14
Is a 1:1 mixture of the (*S,S,S,R*)- and (*R,R,R,R*)- isomers optically active?	yes
Is the (*S,S,R,R*)- stereoisomer dextrorotatory (+) or levorotatory (-)?	cannot predict, experimentally determined
How many achiral stereoisomers are there for this connectivity?	none
The (*R,S,S,R*)- stereoisomer has the same solubility as which stereoisomer?	the (*S,R,R,S*)- isomer
The (*S,S,R,R*)- stereoisomer has an $[a]_D = -55^\circ$; what about (*R,R,R,S*)-?	cannot predict, experimentally determined
How many optically inactive diastereomers does the (*R,S,S,S*)- isomer have?	none
Is a 1:2 mixture of the (*S,S,S,S*)- and (*R,R,R,R*)- isomers optically active?	yes

B. Molecules with More Than One Chiral Stereocenter (Symmetrical, Similar Centers)

A few examples of molecules with two similar chiral stereocenters were shown in Figure 0542, and we return to these separately because the general analysis for two dissimilar chiral stereocenters needs to be modified to account for the observed outcome.

With two similar chiral stereocenters, the coin toss analogy needs to be modified. Instead of a penny and a nickel, where there are 4 observably different outcomes, two similar stereocenters is comparable to having two identical pennies. Although there are still 4 outcomes, statistically, there are only three that are observably different: penny(heads)-penny(heads) and penny(tails)-penny(tails) are clearly different, but penny(heads)-penny(tails) looks the same as penny(tails)-penny(heads). Analogously, the exact same thing happens in molecules with two similar chiral stereocenters: three observable outcomes, that is, three stereoisomers result.

Two of the three stereoisomers are a pair of chiral enantiomers: the "R,R" and "S,S" stereoisomers. The third one is the "R,S" stereoisomer. Because the two chiral stereocenters are similar, this third stereoisomer, with an "R" center that has the exact same composition as the "S" center, is achiral (optically inactive). This stereoisomer, in effect, has a 1:1 ratio of the "R" and "S" geometries of the same four groups, and so it is quite comparable to having a racemic mixture built into a single molecule.

Recall that the test for chirality is whether the mirror image of the object is nonidentical (and therefore chiral) or identical (and therefore achiral). Figure 0547 (found on the next page) gives a side-by-side comparison between the "R,S" stereoisomers of a two dissimilar stereocenter molecule (2-bromo-3-chlorobutane) and the "R,S" stereoisomer of a two similar stereocenter molecule (2,3-dibromobutane). In the chirality test, the mirror image of (2*R*, 3*S*)-2-bromo-3-chlorobutane is (2*S*, 3*R*)-2-bromo-3-chlorobutane, and these are nonidentical. The "R" bromine-containing center can never be identical to an "S" bromine-containing center. On the other hand, the mirror image of (2*R*, 3*S*)-2,3-dibromobutane is just itself (2*R*, 3*S*)-2,3-dibromobutane: Both molecules have one "R" and one "S" bromine-containing center. They are identical structures and represent one achiral stereoisomer.

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Figure 0547

Comparison of chirality tests for a pair of (2*R*,3*S*)-disubstituted butanes, one with two dissimilar chiral stereocenters and one with two similar chiral stereocenters.

two dissimilar chiral stereocenters

2-bromo-3-chlorobutane

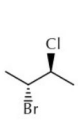
(2*R*,3*S*)-2-bromo-3-chlorobutane

(2*S*,3*R*)-2-bromo-3-chlorobutane

There are two stereoisomers where one stereocenter is "R" and the other is "S", and they are different molecules; the one on the left, above, has the geometry "*R*-bromo, *S*-chloro" and the other one is "*S*-bromo, *R*-chloro."

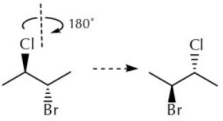
point 1: these molecules are nonidentical because the "R" arrangement at the stereocenter can never be identical to the "S" arrangement

point 2: every "R" arrangement for a given stereocenter one molecule corresponds to the "S" arrangement in the other; these are nonidentical mirror images (enantiomers), and two of the four chiral stereoisomers of the 2-bromo-3-chlorobutane connectivity



(2*R*,3*S*)-2-bromo-3-chlorobutane

mirror plane



(2*S*,3*R*)-2-bromo-3-chlorobutane

a 180° y-axis rotation illustrates that the drawing of the mirror image is not identical to the original drawing, and is identical to the one above, and both of its stereocenters are inverted, as the name indicates

two similar chiral stereocenters

2,3-dibromobutane

(2*R*,3*S*)-2,3-dibromobutane

(2*R*,3*S*)-2,3-dibromobutane

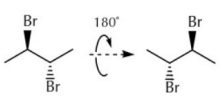
As can be seen by inspecting the names, there is only one stereoisomer where one stereocenter is "R" and the other is "S", and these two drawings are of the same molecule; the one on the left, above, has the geometry "*R*-bromo, *S*-bromo" and the other one is "*R*-bromo, *S*-bromo" also (in the name, *R*-bromo comes before *S*-bromo because the nomenclature tie is broken with alphabetical order, R > S).

point 1: these molecules are identical because they both have identical "R" and "S" arrangements at these two similar stereocenters

point 2: the molecule is identical to its mirror image, and so it is an achiral molecule; but it is one of three stereoisomers of the 2,3-dibromobutane connectivity, where the other two are chiral, which defines this as an example of a *meso* compound

(2*R*,3*S*)-2,3-dibromobutane

mirror plane



(2*R*,3*S*)-2,3-dibromobutane

a 180° x-axis rotation illustrates that the drawing of the mirror image is identical to the original drawing, as the name indicates

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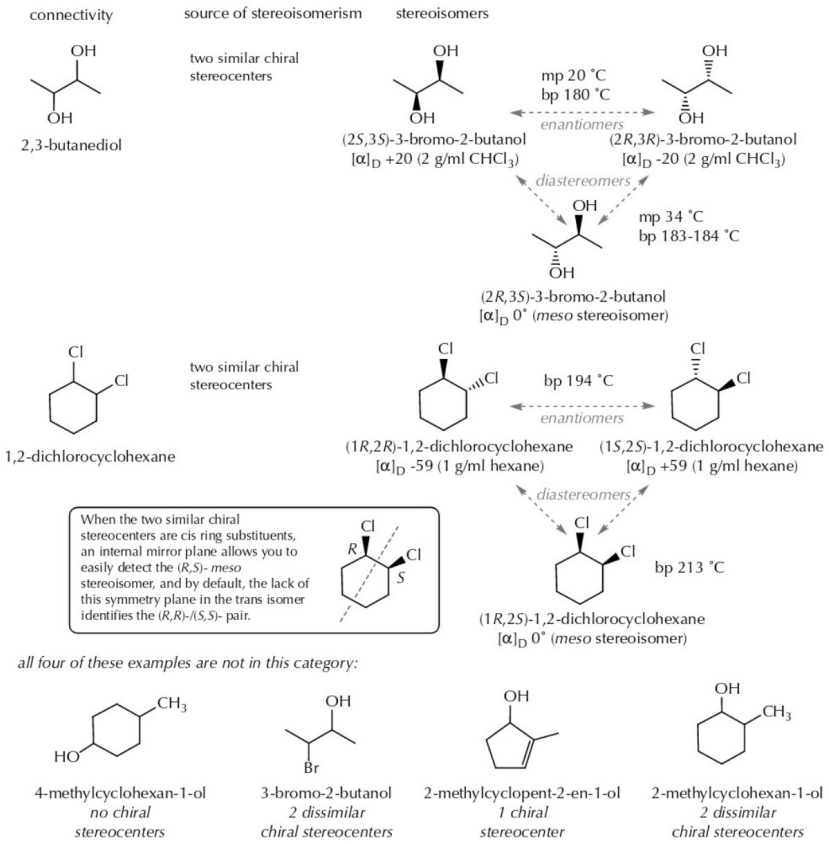
Molecular chirality is a property of the entire molecule, not just a piece of it. So, while this (*2R, 3S*)-2,3-dibromobutane stereoisomer has two genuine chiral stereocenters in it, the entire molecule is itself achiral. Such a molecule has a special name.

An achiral stereoisomer from a collection of stereoisomers where at least one is chiral is called a "meso compound" or a "meso stereoisomer."

In this case, the stereochemical analysis is being carried out on the 2,3-dibromobutane connectivity. There are a total of three stereoisomers, two of which are chiral; thus, this achiral (*2R, 3S*)- stereoisomer is classified as a meso compound. *The term "meso" is not a synonym for achiral, it is a special designation given to the achiral members of a set of stereoisomers that are achiral when at least one of them is chiral.*

Figure 0548

Examples that include analyses for molecules with two similar chiral stereocenters.



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The case of two similar chiral stereocenters is one where meso stereoisomers are most commonly encountered at the introductory level, so careful identification of molecules in this classification is important.

The Bottom Line: For molecules with two similar chiral stereocenters as a source of stereoisomerism, there are three possible stereoisomers. Figure 0548 (on the previous page) summarizes these ideas with examples that both fit and do not fit this classification. Two of the three stereoisomers are chiral ("R,R" and "S,S") while the third is achiral (the "R,S" *meso* compound). There are three pairwise relationships: The "R,R" stereoisomer is the enantiomer of the "S,S" stereoisomer, while the "R,R" stereoisomer and the "S,S" stereoisomer are diastereomers of the "R,S" (*meso*) stereoisomer. As enantiomers, the "R,R"/"S,S" pair will have equal and opposite specific rotations, although the values must be determined experimentally. The "R,S" *meso* compound is optically inactive. Figure 0549 gives another example interrogating a molecule in this classification.

Important and useful note about recognizing meso compounds: When two similar stereocenters are ring substituents, such as in the 1,2-dichlorocyclohexane example in Figure 0548, the isomer with the cis chlorine atoms is easily identified as the unique *meso* stereoisomer because the molecule possesses an internal mirror symmetry plane in which the "R" center reflects the "S" center. This internal mirror symmetry is only possible for the *cis* compound, and so the lack of such an internal mirror plane, as in the two compounds with trans chlorine atoms, also identifies them as the (*R,R*)- and (*S,S*)- pair for the two similar stereocenter case.

Figure 0549

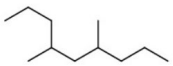
Interrogation of a molecule with two similar chiral stereocenters.

source of stereoisomerism

two similar chiral stereocenters

2,3-butanediol

1,2-dichlorocyclohexane



4,6-dimethylnonane

Question:	Answer:
How many stereoisomers are represented by this connectivity?	three
How many of the 3 stereoisomers are chiral?	two, (*R,R*)- and (*S,S*)-
How many chiral diastereomers does the (*R,R*)- isomer have?	none, it has the one achiral (*R,S*)- *meso*
How many enantiomers does the (*R,R*)- isomer have?	one, the (*S,S*)-
Another stereoisomer is the (*R,S*)-; how many enantiomers does it have?	none, it is the achiral *meso* isomer
How many optically active diastereomers does the (*R,S*)- isomer have?	two, (*R,R*)- and (*S,S*)-
How many optically inactive diastereomers does the (*S,S*)- isomer have?	one, the achiral (*R,S*)- *meso*
Is a 1:1 mixture of the (*S,S*)- and (*R,S*)- isomers optically active?	yes, but only due to the (*S,S*)-
Is the (*S,S*)- stereoisomer dextrorotatory (+) or levorotatory (-)?	cannot predict, experimentally determined
How many achiral stereoisomers are there for this connectivity?	one
The (*R,R*)- stereoisomer has the same solubility as which stereoisomer?	the (*S,S*)- isomer
If the (*R,R*)- stereoisomer has an $[a]_D = +12°$, what about (*R,S*)-?	it is $[\alpha]_D = 0°$; it is achiral, optically inactive

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C. Other Molecules with Multiple Sources of Stereoisomerism

At this point, you now have the tools that can enable you to carry out a stereochemical analysis on millions of different molecules. By carefully identifying and classifying the number and kind of sources of stereoisomerism, you can: (a) tell how many different stereoisomers there are, (b) tell whether they are chiral or achiral, (c) label the geometries, and (d) give the relationship between any given pair of stereoisomers. There are other sources of stereoisomerism than the three introduced so far, and you may encounter some of those others elsewhere, but the general principles established here can be used to understand those other cases.

The three sources of stereoisomerism introduced here (chiral stereocenters with "R" and "S," double bonds with "E" and "Z," and the oppositely-substituted rings with "cis" and "trans") can be mixed and matched in countless ways within diverse molecular structures, and so it is impossible to give a complete list of possibilities because that list is simply too large. And it is completely unnecessary because the principles of stereochemistry are so broadly applicable.

One of the most useful principles is the Le Bel-van't Hoff Rule, because it not only applies to the number (n) of dissimilar tetrahedral stereocenters, but to any collection of dissimilar sources of stereoisomerism. In these cases, all of the statistically possible stereoisomers can form, and you can simply interrogate each one about its properties and relationships.

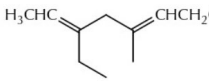
For example, a molecule with a tetrahedral stereocenter ("R" and "S") and two dissimilar double bonds (both with "E" and "Z") has $2^3 = 8$ stereoisomers. All 8 of them only have one chiral stereocenter each, either "R" or "S," so all 8 of them are chiral. The statistical combination of the geometries would give, for example, an "R/E/E" stereoisomer. It would have one enantiomer, the "S/E/E" stereoisomer (note, carefully: the mirror image of an "E" is just itself, not "Z"), and six diastereomers, including, for instance, the "R/E/Z" and "S/Z/Z" stereoisomers.

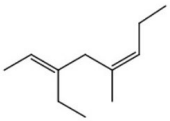
When molecules begin to be more symmetrical, as in the case of two similar stereocenters, then the total number of stereoisomers is invariably reduced from the maximum of 2^n, and *meso* stereoisomers are sometimes formed. There are no generalizations for these special cases, which need to be handled individually.

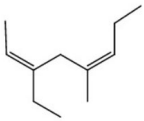
Examples of stereochemical analyses with molecules that have multiple, mixed sources of stereoisomerism are provided in Figures 0550 through 0553. These will give you a good starting point for seeing how the stereochemical principles are applied to some diverse examples.

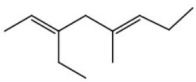
Figure 0550

Stereochemical analyses with molecules that have multiple, mixed sources of stereoisomerism.

connectivity	sources of stereoisomerism	analysis
 3-ethyl-5-methylocta-2,5-diene	two dissimilar double bonds for which (*E*)- and (*Z*)- are possible	2^n is relevant, so there are four stereoisomers: (*E*,*E*)-, (*Z*,*E*)-, (*E*,*Z*)-, and (*Z*,*Z*)- they are all achiral, and any given pairwise comparison is diastereomer


(2*E*,5*Z*)-3-ethyl-5-methylocta-2,5-diene


(2*Z*,5*Z*)-3-ethyl-5-methylocta-2,5-diene


(2*E*,5*E*)-3-ethyl-5-methylocta-2,5-diene

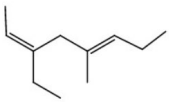

(2*Z*,5*E*)-3-ethyl-5-methylocta-2,5-diene

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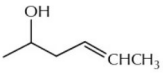
Figure 0551

Stereochemical analyses with molecules that have multiple, mixed sources of stereoisomerism.

connectivity	sources of stereoisomerism	analysis
 4-hexen-2-ol	a chiral stereocenter plus a double bond for which (*E*)- and (*Z*)- are possible	2^n is relevant, so there are four stereoisomers: (*R*,*E*)-, (*S*,*E*)-, (*R*,*Z*)-, and (*R*,*Z*)- they are all chiral; the (*R*,*E*)- is the enantiomer of the (*S*,*E*)-, and the (*R*,*Z*)- is the enantiomer of the (*S*,*Z*)-, while the other pairings are all diastereomers

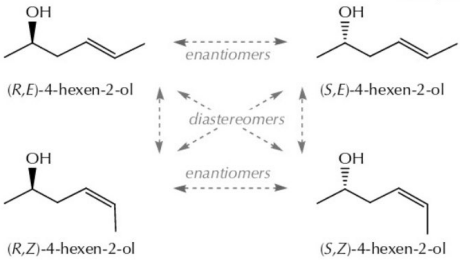
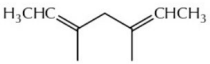
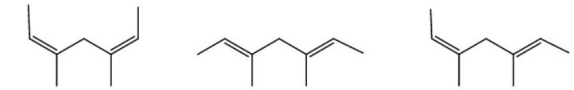


Figure 0552

Stereochemical analyses with molecules that have multiple, mixed sources of stereoisomerism.

connectivity	sources of stereoisomerism	analysis
 3,5-dimethylhepta-2,5-diene	two similar double bonds for which (*E*)- and (*Z*)- are possible	the 2^n maximum is reduced because of similarity; there are three stereoisomers: (*E*,*E*)-, (*Z*,*Z*)-, and only one (*Z*,*E*)-, they are all achiral, and any given pairwise comparison is diastereomer



(2*Z*,5*Z*)-3,5-dimethylhepta-2,5-diene

(2*E*,5*E*)-3,5-dimethylhepta-2,5-diene

(2*Z*,5*E*)-3,5-dimethylhepta-2,5-diene

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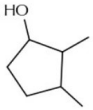
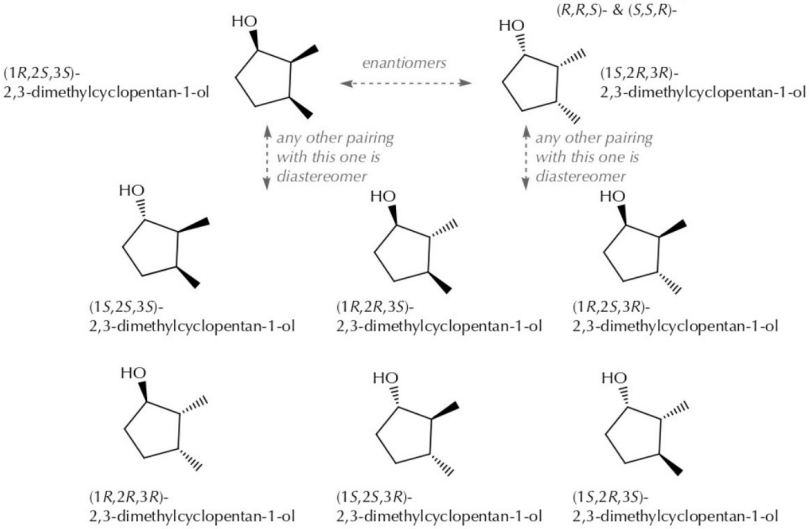
Figure 0553

Stereochemical analyses with molecules that have multiple, mixed sources of stereoisomerism.

connectivity	sources of stereoisomerism	analysis
 2,3-dimethylcyclopentan-1-ol	three dissimilar chiral stereocenters	2^n is relevant, so there are eight stereoisomers, with 4 pairings that are enantiomers and all other pairings being diastereomers; enantiomer pairings: (*R*,*R*,*R*)- & (*S*,*S*,*S*)-; (*S*,*R*,*R*)- & (*R*,*S*,*S*)-; (*R*,*S*,*R*)- & (*S*,*R*,*S*)-; and (*R*,*R*,*S*)- & (*S*,*S*,*R*)-



D. From Molecular Formula to Structural Isomers to Stereoisomers

We have reached the endpoint of how structural variation can produce different molecules. You have not seen all of the individual cases of stereoisomerism, but they are all under that same category of structural analysis.

Stepping back for a moment, if you are given a molecular formula, such as $C_6H_{12}O_2$, part of the 200-year history of organic chemistry can be reviewed by thinking about how many different structures are represented, what their relationships and properties are, and how they might be identified.

From the molecular formula, you can conclude that there is one unit of unsaturation. This might be a carbon-carbon double bond, a carbon oxygen double bond, or a ring of atoms that might include 0, 1, or 2 oxygen atoms. These are the structural isomers: different molecules on the basis of different connectivities.

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From a given connectivity, you can do a stereochemical analysis to decide if the connectivity is unique (no stereoisomers) or whether the connectivity represents a collection of stereoisomers. Once you identify and categorize the source(s) of possible stereoisomerism, you can conclude how many stereoisomers there are, whether or not they are chiral, how to name them and label their relationships.

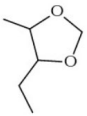
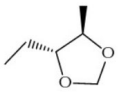
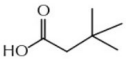
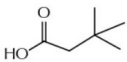
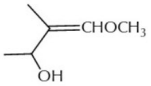
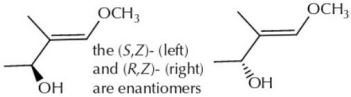
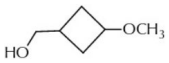
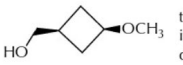
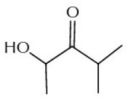
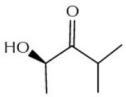
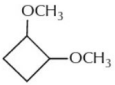
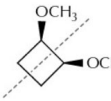
From a specific molecule, you can provide a name that identifies its unique structure, and you can provide the analysis of its molecular symmetry for equivalent and nonequivalent groups of carbon and hydrogen atoms, which would predict what would be observed in the ^{13}C-NMR and ^{1}H-NMR spectra.

Some examples of stepping through this process, starting with $C_6H_{12}O_2$, are provided in Figure 0554.

Figure 0554

From a molecular formula to structural isomers to stereoisomers.

molecular formular $C_6H_{12}O_2$ - one unit of unsaturation: a double bond or a ring

some possible connectivities *structural isomers*	sources of stereoisomerism *stereoisomers*	examples of detailed information
	2 dissimilar chiral stereocenters: 4 chiral stereoisomers (*R,R*)-, (*S,S*)-, (*R,S*)-, (*S,R*)-	 the (*R,R*)- stereoisomer; it has 1 enantiomer and 2 chiral diastereomers
	no source of stereoisomers: 1 unique structure	 4 ^{13}C-NMR signals 3 ^{1}H-NMR signals ratio [1:2:9]
	1 chiral stereocenter and 1 double bond with E/Z: 4 chiral stereoisomers (*R,E*)-, (*S,E*)-, (*R,Z*)-, (*S,Z*)-	 the (*S,Z*)- (left) and (*R,Z*)- (right) are enantiomers
	even sized ring with substituents at the opposite vertices: 2 achiral stereoisomers (*cis*)-, (*trans*)-	 the (*cis*)- stereoisomer; it has 1 achiral diastereomer
	1 chiral stereocenter: 2 chiral stereoisomers (*R*)-, (*S*)-	 the (*R*)- stereoisomer; its specific rotation [α] value and sign cannot be predicted, but it will be equal and opposite that of the (*S*)- isomer
	2 similar chiral stereocenters: 3 stereoisomers, 2 chiral (*R,R*)-, (*S,S*)-, and 1 achiral meso (*R,S*)-	 the cis-disubstituted ring immediately identifies this as the achiral *meso* (*R,S*)- stereoisomer because of the internal mirror plane

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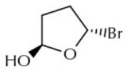
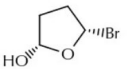
PRACTICE QUESTIONS

5.22 For each of the following pairs of structures (**A** and **B**), tell whether the molecules are identical structures, stereoisomers, structural isomers, or molecules with different molecular formulas. In every case, indicate the stereoisomeric relationship (enantiomer, diastereomer, not applicable) and which of the molecules is expected to be optically active.

(a)

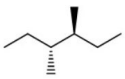
	A	B	
identical			enantiomers
stereoisomers			diastereomers
structural isomers			not applicable
different formulas			optically active

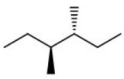




(b)

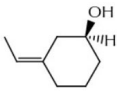
	A	B	
identical			enantiomers
stereoisomers			diastereomers
structural isomers			not applicable
different formulas			optically active

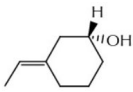




(c)

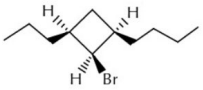
	A	B	
identical			enantiomers
stereoisomers			diastereomers
structural isomers			not applicable
different formulas			optically active

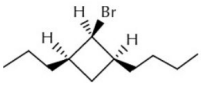




(d)

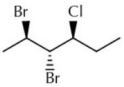
	A	B	
identical			enantiomers
stereoisomers			diastereomers
structural isomers			not applicable
different formulas			optically active

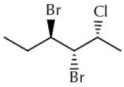




(e)

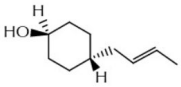
	A	B	
identical			enantiomers
stereoisomers			diastereomers
structural isomers			not applicable
different formulas			optically active

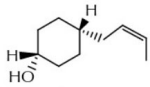




(f)

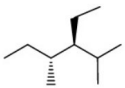
	A	B	
identical			enantiomers
stereoisomers			diastereomers
structural isomers			not applicable
different formulas			optically active

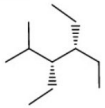




(g)

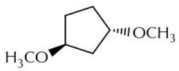
	A	B	
identical			enantiomers
stereoisomers			diastereomers
structural isomers			not applicable
different formulas			optically active

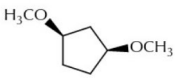




(h)

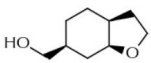
	A	B	
identical			enantiomers
stereoisomers			diastereomers
structural isomers			not applicable
different formulas			optically active

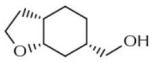




(i)

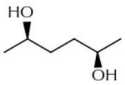
	A	B	
identical			enantiomers
stereoisomers			diastereomers
structural isomers			not applicable
different formulas			optically active

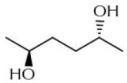




(j)

	A	B	
identical			enantiomers
stereoisomers			diastereomers
structural isomers			not applicable
different formulas			optically active





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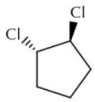
5.23 Answer the questions associated with this particular structure.



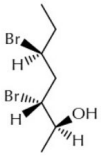
(a) What is the complete IUPAC name for this compound?

(b) Is this molecule optically active? Why or why not?

(c) How many other stereoisomers are there for this connectivity? Explain.

(d) How many achiral diastereomers does this molecule have? Explain.

5.24 Answer the questions associated with this particular structure.



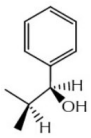
(a) What is the complete IUPAC name for this compound?

(b) Is this molecule optically active? Why or why not?

(c) How many other stereoisomers are there for this connectivity? Explain.

(d) How many chiral diastereomers does this molecule have? Explain.

5.25 Answer the questions associated with this particular structure.



(a) What is the complete IUPAC name for this compound?

(b) Is this molecule optically active? Why or why not?

(c) How many other stereoisomers are there for this connectivity? Explain.

(d) How many diastereomers (chiral and achiral) does this molecule have? Explain.

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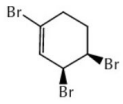
5.26 Answer the questions associated with this particular structure.



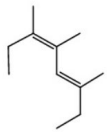
(a) What is the complete IUPAC name for this compound?

(b) Is this molecule optically active? Why or why not?

(c) How many other stereoisomers are there for this connectivity? Explain.

(d) How many chiral diastereomers does this molecule have? Explain.

5.27 Answer the questions associated with this particular structure.



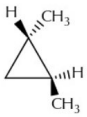
(a) What is the complete IUPAC name for this compound?

(b) Is this molecule optically active? Why or why not?

(c) How many other stereoisomers are there for this connectivity? Explain.

(d) How many achiral diastereomers does this molecule have? Explain.

5.28 Answer the questions associated with this particular structure.



(a) What is the complete IUPAC name for this compound?

(b) Is this molecule optically active? Why or why not?

(c) How many other stereoisomers are there for this connectivity? Explain.

(d) How many diastereomers (chiral and achiral) does this molecule have? Explain.

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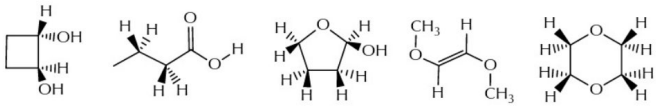
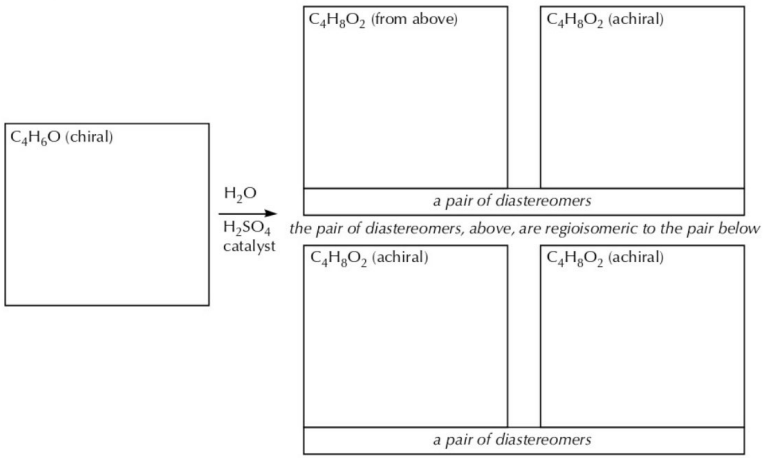
5.29 The following structures represent only a few of the possible structural isomers and, in some cases stereoisomers, of $C_4H_8O_2$. The following statements describe the properties of some of these compounds, or ask a question about the specific molecule shown here. Reply accordingly.



(a) Is a chiral compound					
(b) Is a *meso* compound					
(c) Has a *meso* diastereomer					
(d) Has at least one diastereomer					
(e) Has a pK_a value < 5					
(f) Has 2 signals in its ^{13}C-NMR spectrum					
(g) Has 3 signals in its ^{1}H-NMR spectrum					
(h) Has at least one (*R*)- stereocenter					

(i) In theory, there is a chiral C_4H_6O molecule that can undergo electrophilic addition of water (H_2O/H_2SO_4 catalyst) to give four possible products (two regioisomers, each representing a pair of diastereomers). Three of the four products are achiral, and other product is among the five molecules shown above. Complete the following reaction scheme according to this information.



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Reflections About Science: The Same and Not the Same

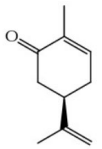
In 1995, Cornell chemistry professor and Nobel Laureate Roald Hoffmann published a book titled "The Same and Not the Same" (Columbia University Press). The text is a broad discussion about dualities in science, and the title reflects the tension Hoffmann sees, sometimes, when scientific and societal obligations are in conflict. The title is also a beautiful summary for an introduction to stereochemistry, in which we deal with stereoisomers: molecules that are at the same time "the same" (connectivity) and "not the same" (geometry).

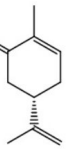
The Enantiomers of Carvone

We use plant-based products for many purposes, including for their flavorings as spices and herbs. We also use what are called the "essential oils" of some plants, which are obtained by chopping, grinding and/or pressing the plants or their seeds to release the oily liquid materials contained in them (almond oil, olive oil, sunflower oil). Sometimes the plant materials are steeped in water-alcohol solutions and the flavoring components are dissolved to make extracts (vanilla, peppermint, orange). Both of the enantiomers of a molecule called carvone are found in nature (Figure 0555). The (*S*)-carvone is dextrotatory, has a strong, spicy odor, and is found at levels of 40–70% in the oils pressed from caraway seeds and dill seeds. The (*R*)-carvone, which is levorotatory, has a relatively light and sweet odor, and makes up to 80% of the oil pressed from many species of mint leaves, particularly spearmint.

Figure 0555
The enantiomers of carvone

(*R*)-carvone
spearmint oil
mp 25 °C
bp 231 °C
$[a]_D$ -61°





(*S*)-carvone
caraway seed oil
mp 25 °C
bp 231 °C
$[a]_D$ +61°

The majority of humans perceive the odors of caraway and spearmint quite differently. And because these two substances are made up of molecules that are enantiomers of one another, the most compelling explanation is that the receptor sites we use are also chiral. Using the analogy from earlier in this chapter: If your nose is filled with receptors that are empty, right-hand gloves, then the way these gloves interact with a right-handed molecule could be significantly different than the way they interact with a left-handed one. So as these left- and right-handed molecules dock with a chiral receptor site, the interactions are different, sending different signals to the brain that are then interpreted as different odors. There are estimates that between 10–30% of people cannot or cannot easily distinguish between the two carvone odors, which could point to mutation-variation in the receptors. In reality, it is quite unlikely that we all perceive the strength of quality of flavors and odors the same way in the first place. At least one other mammalian species, the squirrel monkey, has been observed to distinguish the carvone enantiomers.

The Enantiomers of Thalidomide

During a research project designed to identify new antibiotics, some German scientists discovered the compound named thalidomide in 1953. During testing, although it did not show antibiotic properties, it did show strong and positive sedative properties without some of the common psychoactive side effects. It was introduced into the market as a sedative in 1956. Thalidomide was also found to be particularly effective in reducing the effects of morning sickness in pregnancy, and it become available for this purpose in late 1957.

At this time in history, the drug testing and approval process was much less thorough than it is today. Testing on fetuses and newborns was almost unknown, given the prevalent belief that compounds could not

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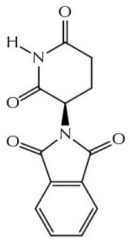
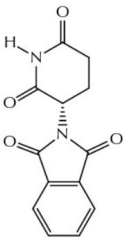
pass through the placental barrier. As it turned out, both of these issues combined to result in a horrible tragedy. At the time, new drugs were not tested for teratogenic (causing birth defects) effects, and human trials were not required. The drug was administered as a racemic mixture, in great part because preparing a single enantiomer is exceptionally more expensive. There was also a general belief that only one enantiomer was bioactive, because of the selectivity for chiral molecules in the body, and that the other would be harmlessly excreted. Although the (*R*)-thalidomide had its positive effects on an adult, both enantiomers did indeed get passed on to the developing fetus where the (*S*)-thalidomide ends up acting as a severe teratogen (Figure 0556).

Figure 0556

The enantiomers of thalidomide

(*R*)-thalidomide
sedative
mp 270 °C
bp 510 °C
$[a]_D$ +63°





(*S*)-thalidomide
severe teratogen
mp 270 °C
bp 510 °C
$[a]_D$ -63°

A sharp increase in babies born with significant physical defects, among whom there was up to a 50% mortality rate, was not associated with thalidomide right away. It would take a couple of years to track down this problem, although it was removed from the over-the-counter market in late 1959 because some adults were showing neurological side effects. Thalidomide was still available by prescription, and its distribution was being advocated in the UK, Australia, and New Zealand, where it was prescribed, and in North America.

Drug approval in the United States is done by the Food and Drug Administration (FDA). In the late 1950s, the entire FDA had only seven individuals, some who were part time workers, who handled all of the new drug reviews. Testing was typically carried out by the companies, who forwarded their results along with the request to bring a new drug to market. In 1960, the reviewer who got the thalidomide approval request for the FDA, Frances Oldham Kelsey, did not rely on the drug company's information, which did not even include any test results. She called upon the company to carry out and report drug testing, and they did not comply—six times! Kelsey held the line against some strong corporate pressure to approve the use of thalidomide, including doing her homework by carrying out a thorough search for any published studies. She uncovered evidence, in published reports of research done in the UK, of unexplained side effects, which strengthened her conviction and her position for more thorough testing prior to approval.

Ultimately, the FDA did not approve thalidomide for distribution in the United States. Unfortunately, there were still at least 17 cases of thalidomide-related birth defects in the US because over 2.5 million doses had been distributed to over 1,000 physicians who were involved in some of the testing that was being carried out. Within a few months after thalidomide's approval in Canada, during early 1961, reports and warnings about its correlation with the birth defects and fatalities were beginning to circulate, although it took a year before it was banned outright and the remaining inventory was ordered to be destroyed.

In 1962, President Kennedy honored Frances Oldham Kelsey with the *President's Award for Distinguished Federal Civilian Service*, in recognition of her courageous scientific convictions in single-handedly forestalling the introduction of thalidomide into the United States. In 2010, she was awarded the first *Frances Kelsey Drug Safety Award*, now an annual recognition by the FDA of exceptional service in support of drug safety. Kelsey's work, and the entire situation surrounding these thalidomide enantiomers, led directly to the significant improvement of drug testing requirements in the FDA approval process.

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Thalidomide represents the tension that Hoffmann writes about in his book. Thalidomide is now known to be an effective drug that relieves pain in severe cases of Hansen's Disease (formerly called Leprosy), and in AIDS patients. It can still be prescribed for individuals who are incapable of becoming pregnant, and a month's supply can be prescribed for those who can become pregnant but test negative. Hoffmann argues that the risks of keeping thalidomide available in the biosphere are too high, regardless of the benefits to these populations, and that there is no way to create global, foolproof regulations—particularly if people with malicious intent want to capitalize on others. You are invited to read more about this important debate.

Summary

Molecules can differ in three ways. First, they can have different molecular formulas, which simply makes them completely different from one another. Second, they can have the same molecular formula, but differ according to connectivity; these are structural isomers. Third, some molecules can have the same connectivity and still differ because of fixed, spatial arrangements at stereogenic atoms called stereochemical configuration.

Three sources of stereochemical configuration were introduced: tetrahedral stereocenters with the "R" and "S" geometries, double bonds with the "E" and "Z" geometries, and symmetrical, even-numbered rings that are substituted at opposite vertices and labeled with the "trans" and "cis" geometries when comparing a pair of hydrogen atoms. Molecules with n sources of stereoisomerism will have 2^n stereoisomers unless the number is reduced by molecular symmetry.

A molecule can be chiral, possessing a nonidentical mirror image stereoisomer called its enantiomer, or it can be achiral. Molecules with one stereocenter create a pair of chiral molecules: the "R" and "S" arrangements are nonidentical mirror images. Each molecule in a pair of enantiomers is chiral, and they have identical physical properties except that they rotate a plane of polarized light in opposite directions (called optical activity). The sign and magnitude of a molecule's specific rotation needs to be determined experimentally and cannot be inferred from its geometry. A mixture of equal amounts of two enantiomers has no optical activity and is called a racemic mixture.

The relationship between any pair of stereoisomers for a given connectivity that is not "enantiomer" is called "diastereomer." Two molecules differing only by an "E" versus "Z" double bond in them are achiral, and they are diastereomers, as are the class of molecules with even-numbered rings and a cis versus trans geometry of substituents on the opposite vertices. Diastereomers have different physical properties. Molecules with multiple stereocenters can have stereoisomers with the diastereomer relationship. An achiral stereoisomer in a collection of stereoisomers where at least one of them is chiral, is called a *meso* compound. The "R,S" stereoisomer in the case of molecules with two similar stereocenters is an example of a *meso* compound.

The rules of organic nomenclature allow a molecule's unique structure, including stereochemical configuration, to be given a name.

Experimentally, it is possible to detect the number of equivalent and nonequivalent sets of carbon atoms in an organic molecule, using ^{13}C-NMR spectroscopy to count the number of absorption signals. The same can be done for sets of hydrogen atoms, using ^{1}H-NMR spectroscopy, in which case it is also convenient to integrate the signals and obtain the relative ratio of the numbers of hydrogen atoms in those sets. The position of the signal in both forms of NMR spectroscopy, called the chemical shift, gives the proximity of the atom(s) to a source of electronegativity. In combination with a molecular formula and some information about the chemical reaction, NMR spectroscopy is a powerful tool for helping to determine the molecular structure of organic molecules.

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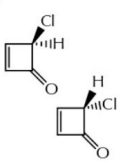
CHAPTER QUESTIONS

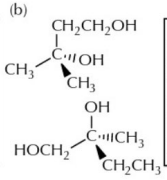
5.30 For each of the following pairs of molecules, check all of the classifications/relationships that apply.

(a)



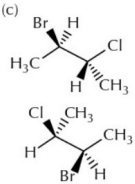
- ☐ enantiomers
- ☐ the same molecule
- ☐ diastereomers
- ☐ constitutional isomers
- ☐ stereoisomers
- ☐ different molecules
- ☐ both are optically active

(b)



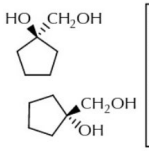
- ☐ enantiomers
- ☐ the same molecule
- ☐ diastereomers
- ☐ constitutional isomers
- ☐ stereoisomers
- ☐ different molecules
- ☐ both are optically active

(c)



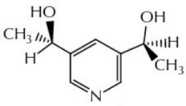
- ☐ enantiomers
- ☐ the same molecule
- ☐ diastereomers
- ☐ constitutional isomers
- ☐ stereoisomers
- ☐ different molecules
- ☐ both are optically active

(d)



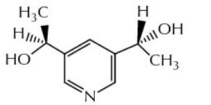
- ☐ enantiomers
- ☐ the same molecule
- ☐ diastereomers
- ☐ constitutional isomers
- ☐ stereoisomers
- ☐ different molecules
- ☐ both are optically active

5.31 Answer the questions about compounds **J** and **K** with respect to compound **H** (*Org Lett*, **2003**, *5*, 3947).



compound **H**

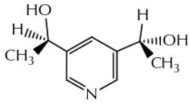
(a)



compound **J**

- ☐ is the enantiomer of **H**
- ☐ has an *S* center and an *S* center
- ☐ the same molecule as **H**
- ☐ is a diastereomer of **H**
- ☐ is optically inactive
- ☐ is a *meso* isomer
- ☐ has an *R* center and a *S* center
- ☐ is optically active
- ☐ has an *R* center and an *R* center

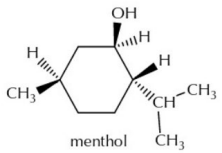
(b)



compound **K**

- ☐ is the enantiomer of **H**
- ☐ has an *S* center and an *S* center
- ☐ the same molecule as **H**
- ☐ is a diastereomer of **H**
- ☐ is optically inactive
- ☐ is a *meso* isomer
- ☐ has an *R* center and a *S* center
- ☐ is optically active
- ☐ has an *R* center and an *R* center

5.32 Menthol is a naturally occurring compound found in the oils of the mint tree *Mentha arvensis*. Menthol is well known for its cooling effects and its mint flavor and odor, which are the basis of the majority of its uses. The single largest use for menthol is probably in cigarettes. A survey of pharmaceutical products indicates that menthol is formulated in over-the-counter rubs and liniments (2–10% concentrations), antipruritic lotions, nasal sprays, expectorants, mouthwashes and sprays, cough drops, and foot powders.



menthol

Provide the complete IUPAC name for menthol.

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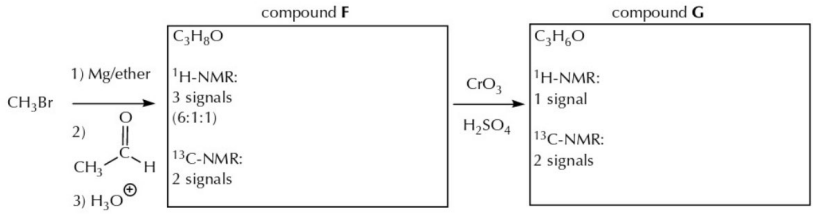
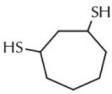
5.33 The following sequence involves unfamiliar chemistry. That's okay, because you have the molecular formulas and NMR data to help you determine the structures of compounds **F** and **G**.



5.34 Answer the following questions about compound **K**.



compound **K**

(a) If $CH_3CH_2CH_2SH$ is named 1-propanethiol, and $HOCH_2CH_2OH$ is named 1,2-ethanediol, then what is the name of compound **K** (connectivity only)?

(b) Draw two different diastereomers of compound **K** (use line/dash/wedge drawings) and answer the following.

stereoisomer **K-1**

stereoisomer **K-2**

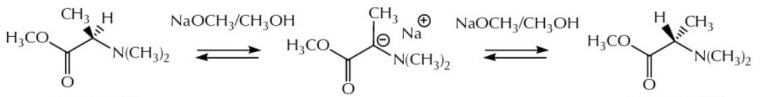
i. Which of your two isomers is/are chiral molecules?

ii. How many diastereomers does stereoisomer **K-1** have?

iii. How many enantiomers does stereoisomer **K-2** have?

iv. Not including stereosiomers **K-1** and **K-2**, how many other optically active stereoisomers of compound **K** are there?

5.35 When compound **L** is treated with a base and conjugate acid mixture ($NaOCH_3$ in CH_3OH), the following isomerization takes place, establishing an equilibrium between Compounds **L** and **M**.



compound **L** compound **M**

At equilibrium, what is the value of the equilibrium constant for K_{EQ} = [**L**]/[**M**]?	Briefly explain:

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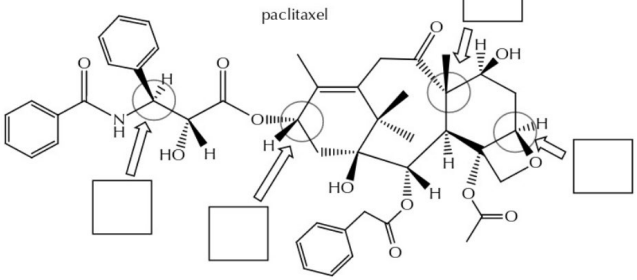
5.36 Taxol is a natural product isolated from *Taxus brevifolia*, the Pacific yew tree. Taxol has been found to be incredibly potent in the treatment of ovarian cancer, and has been FDA approved since 1992. However, a single 100-year-old yew tree only yields 300 mg of paclitaxel (trade name: Taxol), enough for a single treatment. The structure was elucidated in 1971 (*J Am Chem Soc*, **1971**, *93*, 2325) and has been synthesized a number of times.

(a) Provide the (*R*)- or (*S*)- label for each of the four circled stereocenters.

paclitaxel

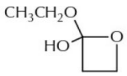


(b) Including these four, how many chiral stereocenters are there in Taxol?

(c) How many chiral diastereomers does this stereoisomer of Taxol have?

Interesting Taxol Fact: Julius Caesar mentions that Catuvolcus, a chieftain of the rival Eburonee nation, committed suicide by consuming extracts from a yew tree. It is presumed that Taxol and other related cytotoxic (toxic to living cells) compounds in this extract were the active compound in his death.

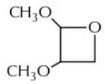
5.37 Answer the following questions about the connectivity of these four $C_5H_{10}O_3$ structural isomers.



compound **W**

(a) How many optically active stereoisomers are there for compound **W**?

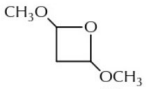
(b) How many signals are there in the ^{13}C-NMR spectrum for compound **W**?



compound **X**

(c) How many optically active stereoisomers are there for compound **X**?

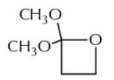
(d) How many signals are there in the ^{13}C-NMR spectrum for compound **X**?



compound **Y**

(e) How many optically active stereoisomers are there for compound **Y**?

(f) How many signals are there in the ^{13}C-NMR spectrum for compound **Y**?



compound **Z**

(g) How many optically active stereoisomers are there for compound **Z**?

(h) How many signals are there in the ^{1}H-NMR spectrum for compound **Z**?

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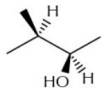
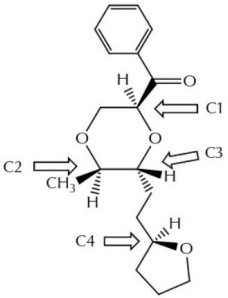
5.38 Provide the complete IUPAC name for this molecule, including stereochemistry.



5.39 Compound **U** is one of a set of potential drug candidates being studied by the Structural Genomics Consortium. Answer the following questions about compound **U**.



compound **U**

(a) What are the stereochemical configurations at each of the indicated stereocenters?

C1	C2	C3	C4

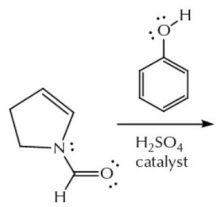
(b) Not counting compound **U**, how many other stereoisomers for this connectivity are there?

(c) How many optically inactive diastereomers does compound **U** have?

(d) How many chiral diastereomers does compound **U** have?

(e) How many enantiomers does compound **U** have?

5.40 Complete the following electrophilic addition reaction to the alkene, as specified.



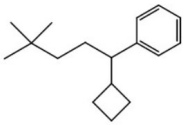
show major regioisomer, "S" configuration

+

show minor regioisomer, "S" configuration

5.41 Draw the structure of the *meso* stereoisomer of 1,3-cyclopentanediol.

5.42 Provide the IUPAC name for the following compound.



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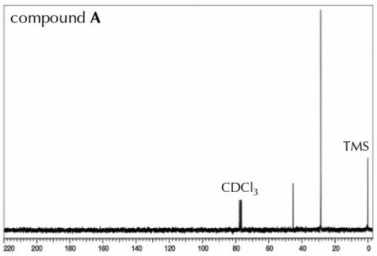
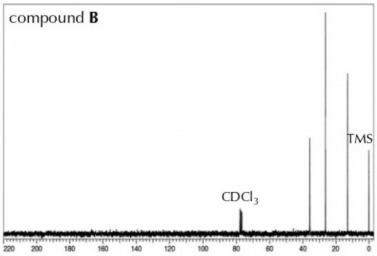
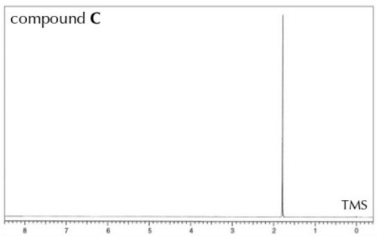
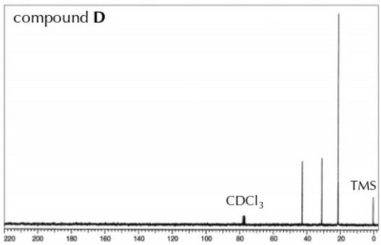
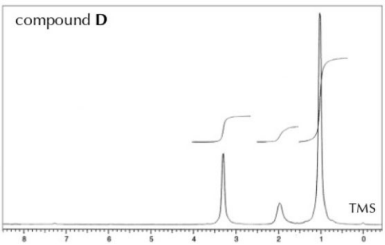
5.43 Keeping good laboratory records is important. Imagine a situation where the indexing on some chemical samples got scrambled. All you know is that the molecular formula for each of these samples is either C_3H_7Br or C_4H_9Br. You also have NMR spectroscopic information about four of the compounds: the ^{13}C-NMR (only) for two of them (compounds **A** and **B**), the ^1H-NMR (only) for one of them (compound **C**), and both the ^{13}C-NMR and ^1H-NMR for the fourth one (compound **D**). As it turns out, taken together, this is enough information to identify compounds **A**, **B**, **C**, and **D**.











compound **A**

Name:

compound **B**

Name:

compound **C**

Name:

compound **D**

Name:

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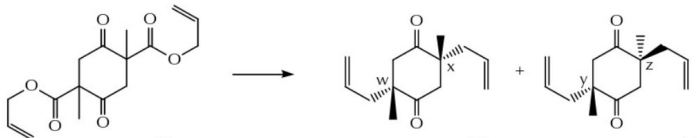
5.44 A class of compounds known as cyanthiwigins, which are isolated from marine sponges, display biological activity against various disease agents, including HIV-1, lung cancer, and leukemia cells. In an improved synthesis of the cyanthiwigins (*Org Lett*, **2016**, *18*, 5720), compound **E** was converted to a mixture of compounds **F** and **G**.



compound **E** compound **F** compound **G**

(a) What are the stereochemical configurational labels for each of these stereocenters?

w: x: y: z:

(b) Answer the following about compounds **F** and **G**.

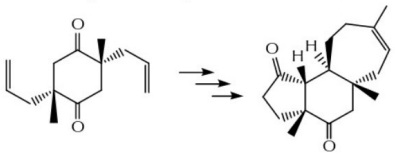
i. Is compound **F** chiral? Explain.

ii. Is compound **G** chiral? Explain.

iii. Is there a stereochemical relationship between compounds **F** and **G**? If so, what is it. If not, why not?

iv. How many other stereoisomers are there with the same connectivity as compounds **F** and **G**? If so, is it (or are they) chiral or achiral?

(c) Later in the synthesis, compound **F** was converted, in many steps, to compound **H**.



compound **F** compound **H**

i. How many other stereoisomers are there of compound **H**?

ii. How many of these other stereoisomers are chiral diastereomers of compound **H**?

(d) Compound **F** is treated with ethanol (CH_3CH_2OH) in the presence of catalytic sulfuric acid (H_2SO_4). Is the reaction at both of the double bonds predicted to have a relatively high regioselectivity (that is, major and minor regioisomers versus roughly equal amounts)? Explain.

(e) Compound **H** is treated with ethanol (CH_3CH_2OH) in the presence of catalytic sulfuric acid (H_2SO_4). Is the reaction predicted to have a relatively high regioselectivity (that is, major and minor regioisomers versus roughly equal amounts)? Explain.

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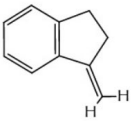
5.45 Provide the structures for the compounds that are required to complete the following reactions, as directed.

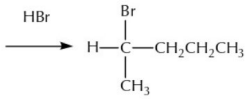
(a)



(*R*)- stereoisomer of the major regioisomer

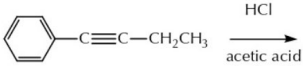
(b)

highly regioselective addition reaction



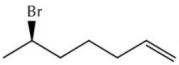
what will be the stereochemical outcome from this reaction?

(c)



(Z)-stereoisomer of the major regioisomer

(d) The major regioisomer resulting from the addition of HBr to optically active (*R*)-(+)-6-bromo-1-heptene has two stereoisomers. Draw these two stereoisomeric products and evaluate what can or cannot be predicted about the optical activity of both products.

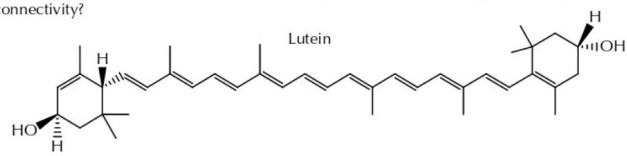


optically active?
why or why not?

optically active?
why or why not?

5.46 Lutein is the compound responsible for the yellow color of autumn leaves that appears when the green of chlorophyll is broken down. It is also responsible for the yellow color of egg yolks. This stereoisomer is one of how many total stereoisomers represented by this connectivity?

Lutein



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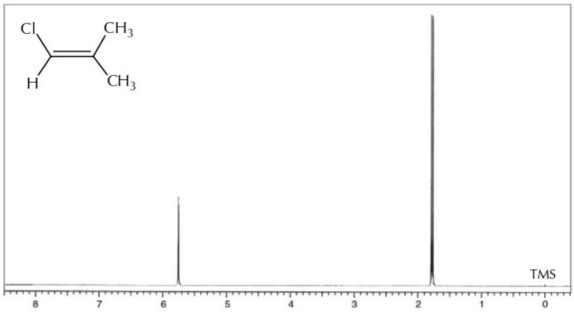
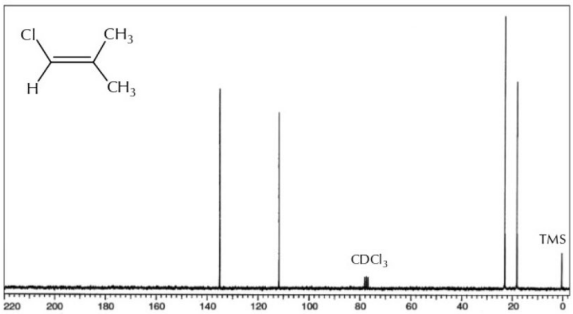
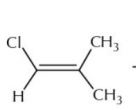
5.47 The ^{1}H-NMR spectrum of 1-chloro-2-methyl-1-propene shows three signals at δ 5.75, δ 1.78, and δ 1.75 ppm, in a 1:3:3 ratio, respectively. The ^{13}C-NMR spectrum shows four signals at δ 135, δ 112, δ 23, and δ 18 ppm. The experimental evidence suggests that the two methyl groups are nonequivalent. Why is this so?





5.48 The electrophilic addition reaction of HBr to 1-chloro-2-methyl-1-propene gives a major and a minor regioisomer. Tell how ^{13}C-NMR and ^{1}H-NMR spectroscopy could be used to assign the molecular structures.



major regioisomer

minor regioisomer

major regioisomer
number of ^{13}C-NMR signals:

number of ^{1}H-NMR signals:

ratio of ^{1}H-NMR signals:

minor regioisomer
number of ^{13}C-NMR signals:

number of ^{1}H-NMR signals:

ratio of ^{1}H-NMR signals:

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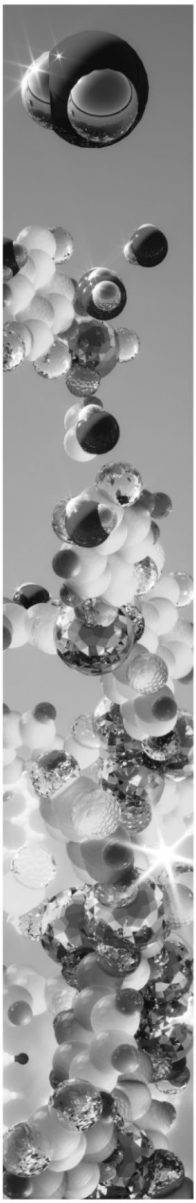

CHAPTER 6

Conformational Analysis of Organic Molecules

Setting the Stage: From Bond Rotations to Molecular Folding—A Grand Challenge

6.1 Bond Rotations Involving Two sp^3 Atoms
- A. Ethane
- B. Butane
- C. 1,2-Dibromobutane and 1,2-Ethanediol
- D. Balancing Competing Factors in Conformational Analysis

PRACTICE QUESTIONS

6.2 Partial Bond Rotations in Small Rings
- A. Cyclopropane
- B. Cyclobutane
- C. Cyclohexane
- D. Substituted Cyclohexanes

PRACTICE QUESTIONS

6.3 Stereoisomerism and Fluxional Behavior
- A. Acyclic Compounds
- B. Cyclic Compounds
- C. Nitrogen, Sulfur, and Phosphorus Stereocenters
- D. Alkenes, Amides, and Esters

PRACTICE QUESTIONS

Reflections About Science: Axial and Equatorial

Summary

CHAPTER QUESTIONS

EXAM QUESTIONS (CHAPTERS 4–6)

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CHAPTER 6

Conformational Analysis of Organic Molecules

Setting the Stage: From Bond Rotations to Molecular Folding—A Grand Challenge

The three-dimensional structure of molecules is complex. Single bonds can rotate freely, and the rotational process takes place with quite low activation energies, which means that the internal parts of a molecule are spinning and folding through all possible angles and forms at a rate of about 10^8–10^9 times per second.

The idea of a molecule that is dynamically changing its shape contrasts greatly with the study of rigid geometries (stereochemistry) in Chapter 5. To set the stage for studying the dynamic changes, we will begin with a few reminders about the rigid shapes of stereoisomers. In stereoisomerism, the different sources of three-dimensional geometry, such as the tetrahedral arrangements of four different groups, stay fixed in place and result in shapes that create different molecules (stereoisomers).

Under normal laboratory conditions, the vast majority of molecules with assignable stereochemical configurations, such as "R" and "S" or "E" and "Z", are effectively locked into these three-dimensional shapes. We think of the four groups in a tetrahedral "R" geometry, for instance, as being in a fixed bonding arrangement. Only a series of bond-breaking and bond-making events could result in turning that "R" geometry into an "S" geometry.

Chemists routinely refer to the permanence of molecular geometry as configurational stability, a hallmark of stereochemistry. Stereoisomers represent geometrical arrangements of molecules that, if purified and kept under typical laboratory conditions, are unchanged on normal timescales (days, years) at "room temperature" (ca. 20 °C), where the bonds at the stereocenters are not breaking and reforming. Chemists often express the idea of a stable molecule in these practical terms: If you isolate a pure sample of something, put it in a bottle, place it on a shelf, and then come back tomorrow—will it still be there? If so, then it is stable.

So far, we have been looking at three-dimensional arrangements that persist under normal conditions. The behavior of the two 3-heptene diastereomers is typical (Figure 0601). You can isolate and store a pure sample of (*E*)-3-heptene for a long time without worrying that the (*Z*)-3-heptene has formed. And vice versa; these molecules are configurationally stable under normal conditions. A bottle of (*E*)-3-heptene today will still be (*E*)-3-heptene tomorrow.

The properties of these two alkenes are also typical. The energy difference between (*E*)-3-heptene and (*Z*)-3-heptene is modest (about 4 kcal/mol), which means that one of them is not extraordinarily more stable than the other one. And in theory, while breaking the pi bond could allow the remaining sigma bond to rotate, interconverting the (*E*)- and (*Z*)- forms, the energy of activation to break the pi bond is quite high (65 kcal/mol). However, energies of activation greater than or equal to about 30 kcal/mol usually make the rate of any transformation taking place at room temperature negligible.

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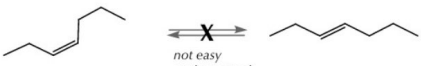
Figure 0601

Configurationally stable and unstable alkenes.

(*E*)- and (*Z*)-3-heptene: configurationally stable

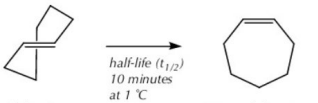


(*E*)-3-heptene
configurationally stable

(*Z*)-3-heptene
configurationally stable

p orbital / p orbital angle = 0°
ΔG° (as shown) = -4 kcal/mol
E_{ACT} (as shown; to break pi bond) = 65 kcal/mol

(*E*)-cycloheptene: configurationally unstable



(*E*)-cycloheptene
configurationally unstable at 1 °C

(*Z*)-cycloheptene
configurationally stable

p orbital / p orbital angle = 30°
ΔG° (as shown) = -30 kcal/mol
E_{ACT} (as shown; to break pi bond) = 17 kcal/mol

On the other hand, there are examples of unstable stereochemical configurations, including an alkene that was discussed in Chapter 5. You may recall (Figure 0518) that the double bond in (*E*)-cycloheptene can break and rotate at 1 °C, with a half-life of 10 minutes, resulting in the more stable (*Z*)-cycloheptene. The (*Z*)-cycloheptene is almost 30 kcal/mol more stable than the (*E*)-cycloheptene. In fact, there is so much angle distortion and strain in (*E*)-cycloheptene that the two pi orbitals of the pi bond are tilted at an angle of about 30°, creating only a weak pi bond compared with the ideal parallel (0°) arrangement for the best pi bonding (i.e., the best orbital overlap).

The upper limit temperature for storing (*E*)-cycloheptene is about -30°C. If you made a pure sample of (*E*)-cycloheptene and stored it away from contaminants in a 1 °C refrigerator, then in one hour, less than 2% of the sample would still be (*E*)-cycloheptene; and overnight (8 hours later), only an undetectable concentration (theoretically 10–13%) would remain. We say that (*E*)-cycloheptene is configurationally unstable under normal conditions.

With those reminders about stereochemistry, we now move to the topic of molecular shapes that are undergoing dynamic changes. Most parts of molecular structures are not rigid but are instead relatively flexible. Strands of atoms can bend and flop around with respect to themselves, which means that molecules exist in a large array of interconverting geometrical shapes, none of which requires bonds to break and form. These different molecule shapes are transient. The motion making the shapes, which is exceptionally fast, results from the low energy process of bond rotations around single bonds. In contrast with the rigid (fixed) shapes called stereochemical configurations (*E/Z, R/S*), the different flexible and rapidly interconverting shapes are called the conformations of the molecule.

Studying the relative energy of conformations as well as how the bond rotations take place, called conformational analysis, is the topic of this chapter.

A molecule with hundreds of atoms is generally going to be able to adopt millions of different shapes compared to smaller molecules. The study of conformations in large molecules (macromolecules) is important because overall molecular shape is a critical part of understanding their properties. In the area of synthetic polymers and plastics, different molecular shapes result in diverse material properties. The difference between long molecular strands that are linear, versus bent, versus interconnected, versus balled up, results in plastics that have quite different observable properties, such as being stretchy, brittle, flexible, or bouncy. Molecular shape plays a role in the difference between the materials that go into a rigid bottle for storing milk or juice and those that make a flexible bag for holding a sandwich, or even the clear plastic wrap you use to package it.

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One of the topics routinely listed today as a Grand Challenge in science is understanding how large biological molecules bend and fold, and how this relates to their biological activity. Enormous amounts of resources are currently being invested in trying to figure out the rules for how large biological macromolecules adopt their shapes. In general, this area is called "the folding problem" as it relates to proteins, RNA, and DNA.

Humans have known for a while now that DNA and RNA are polymers composed of long and linear sequences of individual molecular units (monomers) called nucleic acids, and that proteins are linear sequences of amino acid monomers. These long strands of atoms are comparable to a long string of beads, a power cord for your computer, or the wire from a pair of earphones. Any of these linear strands can be twisted and folded into many different shapes or tangles. We also know that the critical biological function of these molecules is related to their ability to wind into, and maintain, a single overall molecular shape, and to be able to unwind and rewind into the same original state. Imagine a 6-meter-long string of beads where the shape of its tangled-up form is not only predetermined but is also an exact shape into which it can fold and refold when you straighten it out or bend it another way.

The molecular shape of biological macromolecules is a key part to understanding biochemistry. Strands of DNA along with added proteins (together, called chromosomes) are more relatively protected from harm when they are tightly wound up compared to when they are unwound. Various disease states can result from problems with the RNA folding or refolding process. And the specifically folded shapes of certain protein strands, called enzymes, are responsible for catalyzing all of the chemical reactions in every biological system.

Studying molecular folding is a high priority research area. The significance to the health and welfare of humans is potentially profoundly important. Everything from allergies to neurodegenerative diseases has been implicated as deriving from incorrectly folded proteins, and so understanding the normal folding process is key to unlocking the origins of any abnormal processes.

In the 1950s, a scientist named Christian Anfinsen demonstrated that a biologically active protein molecule that facilitates DNA-RNA interaction, bovine pancreatic ribonuclease, could be unfolded by changing its chemical environment (pH, temperature) and that its activity, and so its shape, could be restored upon restoring its environment. His fundamental conclusion still holds, today: The three-dimensional shape adopted by these molecules is coded into their one-dimensional linear sequences and presumes a chemical environment that is complementary to the code (that is, that the environment, a solvent such as water, is not a passive observer but rather plays a role in the folding process).

"How does the 3D structure derive from the 1D linear sequence?" is one of the three questions that commonly define the protein folding problem. These are the questions that scientists are trying to answer, to understand this folding process. The other two questions are: What is the folding mechanism (the pathway for how to get from a 1D strand to the specific 3D structure) and how does it get there quickly? Creating a predictive model for new molecular shapes holds the promise for allowing us to design customized medical treatments. Studies that began in the mid-1990s are still advancing today. In 2020, significant progress was reported in using artificial intelligence (AI) networks to address protein folding.

> "It's a game changer," said evolutionary biologist Andrei Lupas during an interview about recent AI breakthroughs. "This will change medicine. It will change research. It will change bioengineering. It will change everything."
>
> E Callaway, "It will change everything" *Nature*, **2020**, *588*, 203.

The realities of biological systems make understanding the folding problem much more complex than the way Anfinsen's experiments were done, in which he looked at single proteins dissolved at dilute concentrations, where the protein molecules are surrounded by vast amounts of only water. Inside of actual

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human cells, there are an estimated 1–3 billion proteins with up to 20 million copies of any given one of them. All of these molecules are packed together, where winding and unwinding needs to take place without them ever getting tangled up in each other. Imagine the nightmare problem of only 5 sets of electrical cords (the holiday light problem) being tossed inside a big bag and trying to just retrieve one of them from the center of the bundle if they were also free to wind and unwind.

Returning now to the study of single bonds in small organic molecules, which is the main topic of this chapter. At the most fundamental level, the principles that govern the rotation of single bonds in small organic molecules are the first step in building the story for how the one-dimensional linear sequences of DNA, RNA, and proteins result in specific shapes, and how they get there. All of the familiar molecular interactions play relevant roles, too, such as hydrogen bonding, ionic interactions (both favorable and unfavorable), hydrophobic and hydrophilic effects, and so on. While we will look in detail, in this chapter, at only a few processes that are not even close to the complexity of protein folding, remember that this topic, conformational analysis, leads directly to one of the most actively pursued areas of research today.

6.1 Bond Rotations Involving Two sp^3 Atoms

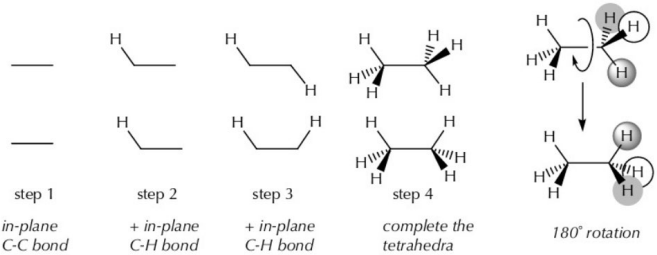
A. Ethane

Important Advice: Using a set of molecular models is incredibly useful for understanding conformational analysis. The 2D visualizations we draw during conformational analysis rely on an even greater level of mental abstraction than in drawing stereoisomers, and so the correlation between a static 2D drawing and the moving 3D shape it represents is more sophisticated.

This will not be the first reminder about the value of molecular models in this chapter. Here are a few generalizations about why learning conformational analysis benefits from constantly using 3D forms to understand what is being drawn in 2D environments. First, compared with stereoisomerism, which was concerned with localized differences in geometry resulting in different molecules, conformations are more complex shapes that cover large segments of molecules, or even the entire molecule. Second, the relative spatial position (near or far, and/or at what angle) of one segment of a molecule relative to another segment is being described. Third, the conformational picture of a molecule is dynamic, involving motions where one shape becomes another through a process of bond rotation. You can spin the bond in a model!

Although ethane is not a complicated molecule, studying its bond rotation forms the foundation for conformational analysis. If you try to draw the two tetrahedral atoms in ethane bonded together using the standard line/dash/wedge drawing method, you end up with two possible representations. With the bond between the atoms drawn in the plane of the writing surface, there are two options for placing the other two in-plane bonds. They are either pointed in the same direction or in opposite directions. The placement of the other four bonding sites follows from the placement of the in-plane bonds (Figure 0602).

Figure 0602
Two different drawings for ethane using line/dash/wedge notation.



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The two individual tetrahedral atoms have fixed configurations. That is, the four specific atoms in either tetrahedral array do not change their positions with respect to one another. But the two tetrahedra are connected by a single bond that can rotate.

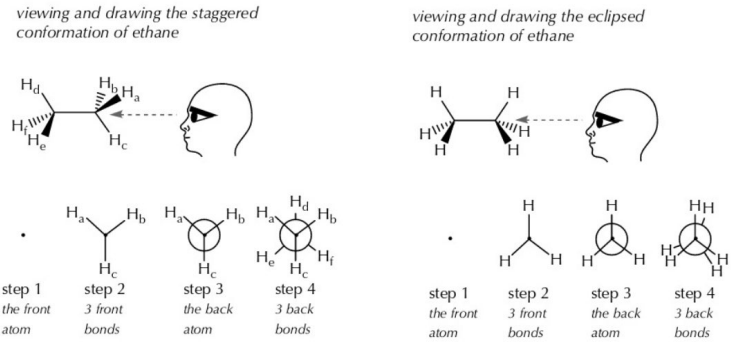
> *One more reminder, already: The dynamic motion of a bond rotation is quite difficult to illustrate using static two-dimensional drawings, but quite easy to demonstrate using physical models. Drawings and diagrams are the way we communicate, and so you must think about these molecules as physical objects whose reality is being represented with simple drawings. The drawings of a molecule are as much a placeholder to talk about the underlying reality of molecules as a drawing of a cat or a dog is a placeholder for the reality of those animals. And no matter how good the drawing is, you can never learn about soft fur, a purr, or a bark without also dealing with the reality. Molecules are even more difficult because you cannot hold them or pet them! Make models and see the connection between them and the drawings we use.*

A standard line/dash/wedge drawing views a molecule from its edge. In the early 1950s, a chemist named Melvin Newman introduced a representation for visualizing the bond rotation by viewing the bond in an end-on manner. These are called Newman projections (Figure 0603).

The eye of the observer is placed along the bond axis, at either end. The cartoon face profile in Figure 0603 illustrates the necessary point of view. The visualization process is exactly the same as that for assigning "R" and "S" labels (see Figures 0526–0528), except that we are now drawing what we see from that perspective. The point of view illustrated by these profiles is commonly expressed using an open eye and an arrow pointing towards the closer of the two atoms in the bond being visualized. In a Newman projection, the closer atom (or front atom, from the direction of view) is represented as a point. The farther atom (or back atom) sits directly behind the front atom, and is represented by a larger circle.

Figure 0603

Constructing Newman projections from line/dash/wedge drawings.


viewing and drawing the staggered conformation of ethane
viewing and drawing the eclipsed conformation of ethane
step 1 the front atom
step 2 3 front bonds
step 3 the back atom
step 4 3 back bonds
step 1 the front atom
step 2 3 front bonds
step 3 the back atom
step 4 3 back bonds

From the viewing perspective, the other three bonding sites (shown as a line, a dash, and a wedge in the original drawing) on the tetrahedral atoms are pointed towards the vertices of an imaginary triangle. If the line (i.e., the in-plane bond) is pointed straight down, then the three bonding sites look like the letter "Y" (see step 2 on the left), and if the line is pointed straight up, then the three bonding sites look like the letter "Y" turned upside down (step 2 on the right). The point of view of the viewer needs to be defined carefully to create the proper Newman projection.

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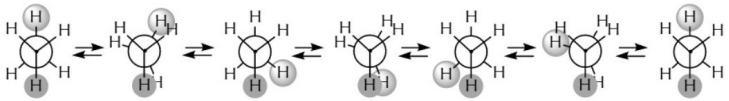
The staggered conformation of ethane. The three bonding sites on the front atom are drawn according to the "Y" shape. On the back atom, the "Y" arrangement is opposite that of the front atom, in which case the six lines for the bonding sites are alternating front/back/front/back every 60° around the Newman projection. This is called a staggered arrangement or staggered conformation of the bonds. As the two in-plane bonds in the original line/dash/wedge drawing are pointed 180° away from each other, then their opposite directions can be readily seen in the staggered conformation, as represented by the Newman projection. What is less obvious in the line/dash/wedge drawing that is immediately clear in the Newman project is that there are two other 180° pairs of bonding sites, corresponding to wedge/dash pairing in the original drawing.

The eclipsed conformation of ethane. Alternatively, the "Y" or upside-down "Y" orientation on the back atom might be the same as the front atom, in which case we say that the front-to-back bonds and atoms are eclipsing each other (an eclipsed conformation). Because it is impossible to see the atoms and bonds in the back that are being eclipsed by those in the front, the back atom is twisted a little bit to the right (clockwise) or a little bit to the left (counterclockwise).

A Newman projection is a drawing that shows the relative spatial position of the six groups attached to two tetrahedral atoms much more easily than in the conventional line/dash/wedge drawings. The central bond can be set into motion, and the change in the relative position of the atoms in the front with respect to the atoms in the back can be visualized. Starting with two of the hydrogen atoms labeled with shaded circles as reference points, 180° apart, a bond rotation is represented in Figure 0604 in which the front atom remains fixed and the back atom is turned clockwise, in 60° increments, until it reaches the original position.

Figure 0604

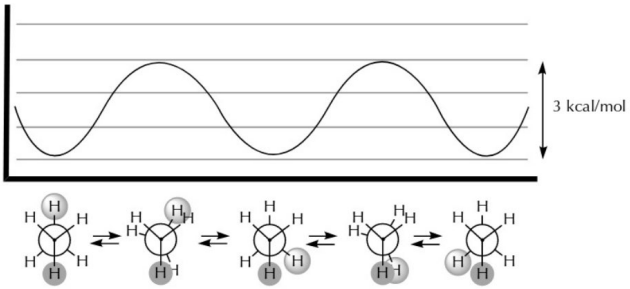
Representing the bond rotation in ethane.



In ethane, the staggered form is more stable than the eclipsed form by 3 kcal/mol. The staggered form represents an energy minimum during a bond rotation, while the eclipsed form is an energy maximum. The change in energy during the bond rotation of ethane can be shown as an energy diagram, where the eclipsed forms are the transition states between the staggered forms. A segment of the energy diagram for the bond rotation of ethane is shown in Figure 0605.

Figure 0605

Energy diagram for part of the bond rotation in ethane.



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The conformational analysis of ethane describes the change in energy that takes place during a bond rotation and includes the explanation for the energy differences. In principle, there are an infinite number of conformations for ethane because the bond rotation takes place smoothly through an infinite number of angles between 0° and 360°. In practice, we generally focus on the three staggered conformations and the three eclipsed conformations as the energy extremes and imagine the actual bond rotation taking place using these shapes as reference points.

In the absence of additional experimental evidence, we also assume that all staggered forms are more stable than all eclipsed forms. Although there is still active debate about why the staggered forms are more stable, the VSEPR model provides sufficient explanation for these examples: Bonds that are eclipsed are aligned as close as possible, and experiencing the greatest electron-electron repulsion, which is unfavorable. The bonds that are staggered are as far away from one another as possible and experiencing the least repulsion, as any given bond on the front atom is nestled between two on the back atom.

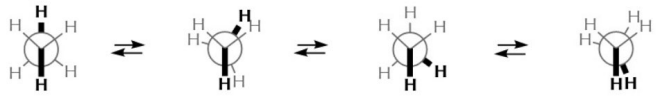
As seen in the energy diagram for the bond rotation (Figure 0605), the eclipsed form is a transition state between any two staggered forms, and the bond rotation has an activation energy of 3 kcal/mol. Under usual conditions (room temperature ~ 20 °C, 70 °F), the Boltzmann Distribution shows that there are molecules with enough energy to allow processes of up to about 20–25 kcal/mol to proceed. This means that there is plenty of available energy for the carbon-carbon bond in ethane, with an activation energy of 3 kcal/mol, to undergo rapid rotation at room temperature.

Although the rotational motion is expected to be occurring freely, a large fraction of the molecules, at any given moment, would be expected to be in or near the more stable staggered conformation. The actual bond rotation, if you could see it, would be jerky, with the molecules jumping from one staggered form to the next, spending the least amount of time at the eclipsed conformation, which is a transition state between the staggered forms.

When examining only staggered and eclipsed forms, the number of angle relationships between the bonds on adjacent atoms is finitely few. In a staggered conformation, any bond you select on one atom has a set of three neighboring bonds on the other atom, one of which is 180° away from it and two others that are 60° away from it. Period. Geometrically, these front-to-back relationships are dihedral angles, defined by 4 points. Newman projections are an extremely useful way to visualize the dihedral relationships. The two dihedral angles in a staggered form are called antiperiplanar (commonly just "anti") for the 180° relationship, and synclinal (commonly just "gauche") for the 60° relationship. In an eclipsed conformation, the two dihedral angles are 0° (synperiplanar, "syn," or simply eclipsed) and 120° (anticlinal or eclipsed). All of these angles are illustrated in Figure 0606.

Figure 0606

Common labels used for dihedral angle relationships.



180°
antiperiplanar
"anti"

120°
anticlinal
eclipsed

60°
synclinal
"gauche"

0°
synperiplanar
"syn"
eclipsed

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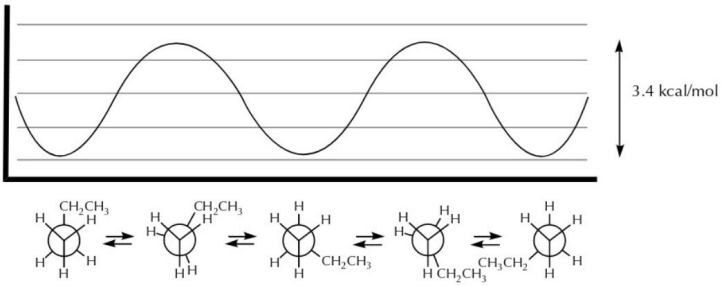
B. Butane

As the number of tetrahedral atoms in a molecule increases, the conformational analysis gets more and more complex to carry out. Without sophisticated computational methods, we tend to limit our analyses, using simple drawings, to one bond at a time.

Butane contains three bonds between tetrahedral atoms (C_1-C_2, C_2-C_3, and C_3-C_4). The conformational analysis for the C_1-C_2 bond is identical to the C_3-C_4 bond because of the symmetry of the molecule. The difference between the eclipsed and staggered conformations (i.e., the activation energy for the bond rotation) is 3.4 kcal/mol (Figure 0607).

Figure 0607

Energy diagram for part of the C_1-C_2 and C_3-C_4 bond rotations in butane.



The C_2-C_3 bond is more interesting, because now there is a methyl group attached at each of the reference atoms for the analysis. A conformational analysis can begin with any one of the geometrical arrangements (conformations), and then continuing with a systematic investigation of the bond rotation: holding one of the atoms fixed while rotating the other in a consistent clockwise or counterclockwise direction, stopping every 60° to represent the next staggered or eclipsed form along the way.

The energy diagram in Figure 0608 starts with the conformation where both of the methyl groups on carbons 2 and 3 of butane sitting in the plane of the writing surface (line/dash/wedge drawing) and with those bonds placed opposite each other in a staggered conformation. That drawing and the Newman projection clearly show the two methyl groups are anti (180° dihedral angle). The bond rotation is shown by turning the back carbon in the clockwise direction, as visualized in the Newman projections. According to the general guidelines, all of the staggered conformations are more stable than the eclipsed forms. Experimentally, the staggered form with the two anti methyl groups (180°) is 0.90 kcal/mol more stable than the two staggered forms when the methyl groups are gauche (60°). The eclipsed conformation in which the methyl groups are syn (0°) is least stable (4.5 kcal/mol above the anti form), while the other two eclipsed forms are 3.8 kcal/mol above the anti form).

The difference in stability between the staggered forms with the anti and gauche methyl groups, as well as the difference in the eclipsed forms, may make a certain amount of intuitive sense: When the methyl groups are closer together, they are behaving like physical objects that are colliding. The methyl groups take up real space, and as they get closer to one another, they cannot occupy each other's physical space. As a result, the molecule undergoes a distortion where bonds are stretched out and/or where angles are distorted (torsional strain) beyond their ideal values (Figure 0609). This repulsive effect is always destabil-

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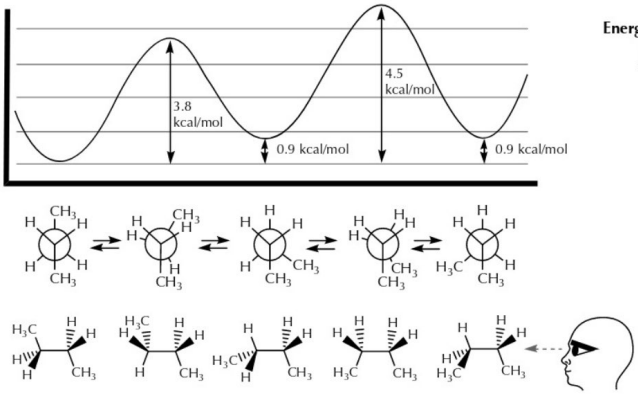
Figure 0608

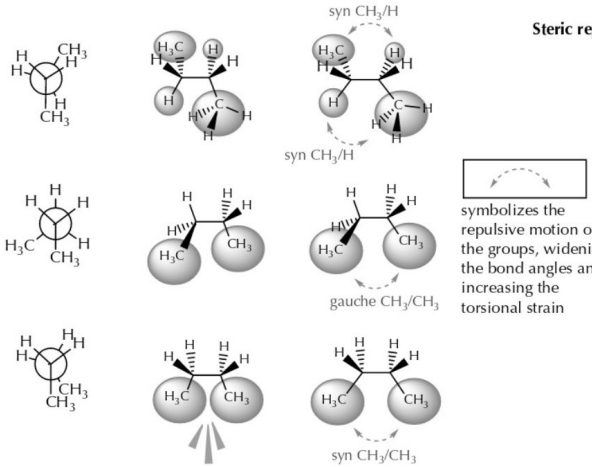
Energy diagram for part of the C_2-C_3 bond rotation in butane.



izing, and it is called (synonymously) steric repulsion, steric hindrance, or steric interference. The larger these groups are, the greater this repulsion is expected to be as they get close to one another during a bond rotation.

Figure 0609

Steric repulsion distorts bond lengths and angles.


syn CH3/H
syn CH3/H
symbolizes the repulsive motion of the groups, widening the bond angles and increasing the torsional strain
gauche CH3/CH3
syn CH3/CH3

The steric hindrance effect is superimposed on the intrinsic difference in stability between the staggered and eclipsed forms. As stated previously: In the absence of additional information, assume that the subset of staggered forms is more stable than the subset of eclipsed forms, and that the additional effects, such as steric repulsion, will sort the conformations within the staggered and eclipsed subsets. This generalization is not a law, and perhaps surprisingly, based upon the discussion so far, there are molecules where the steric hindrance is so severe that an eclipsed conformation can become more stable than a staggered

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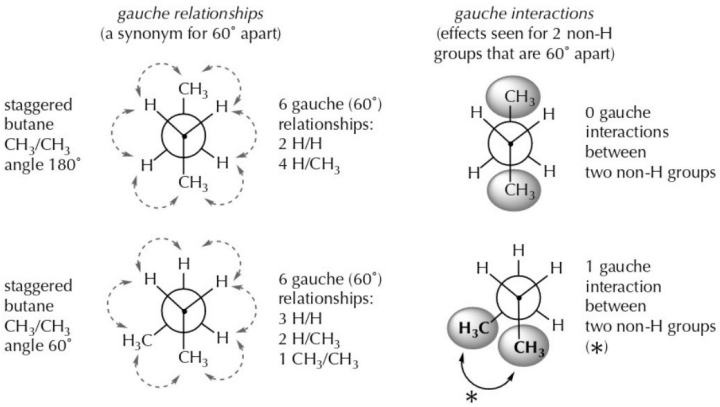
form. This observation is unusual, however, and so we will operate with the assumptions stated above unless there is experimental information to indicate otherwise.

Eclipsed conformations are the transition states between the staggered forms, representing the least populated form that the molecule has. Correspondingly, conformational analyses most often focus on the energy relationships between the three staggered forms. In a staggered conformation, the only two dihedral angle relationships are when two groups are anti (180°) with respect to each other, or when they are gauche (60°). Two groups that are anti are pointed in opposite directions and cannot have any of the traditional intramolecular interactions (e.g., hydrogen bonding), and so we pay more attention to the interactions that can happen when two groups are gauche.

An important note about terminology. The term "gauche" is used in two different expressions: gauche relationship and gauche interaction. Gauche relationship is a general label: *in a staggered conformation, there are six gauche (60°) relationships between adjacent bonds.* Used a different way, in gauche interaction, the two-word term refers to the stabilizing or destabilizing effect between two non-hydrogen atom groups that are in a gauche relationship: *a gauche interaction between the two methyl groups in butane is a destabilizing effect on a conformation due to steric hindrance.* Figure 0610 illustrates this distinction using the two different staggered conformations of butane.

Figure 0610

Gauche relationships versus gauche interactions in staggered butane conformations.


gauche relationships
(a synonym for 60° apart)
gauche interactions
(effects seen for 2 non-H groups that are 60° apart)
staggered butane CH3/CH3 angle 180°
6 gauche (60°) relationships:
2 H/H
4 H/CH3
0 gauche interactions between two non-H groups
staggered butane CH3/CH3 angle 60°
6 gauche (60°) relationships:
3 H/H
2 H/CH3
1 CH3/CH3
1 gauche interaction between two non-H groups (*)

C. 1,2-Dibromobutane and 1,2-Ethanediol

Steric hindrance is a gauche interaction that is only destabilizing (repulsive). Over the years, as the field of conformational analysis matured, gauche interactions beyond steric hindrance were needed to explain a variety of experimental results. In particular, there were cases where gauche interactions sometimes needed to be an attractive (stabilizing) force instead of a repulsive one.

A summary of the four most common classes of gauche interactions you need to look for when carrying out a conformational analysis is provided in Figure 0611. Two of them (steric hindrance, charge/charge repulsion) are destabilizing (repulsive) and favor the anti relationship of those groups, while two of them (hydrogen bonding, charge/charge attraction) are stabilizing (attractive) and favor the gauche relationship of those groups.

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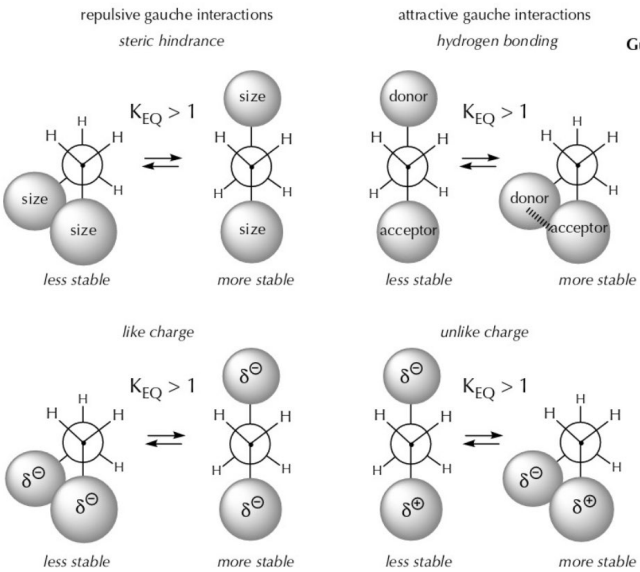

Figure 0611
Guidelines for carrying out conformational analysis: gauche interactions.

In the absence of conflicting information, you may assume that all staggered forms are more stable than all eclipsed forms. Sorting the relative energies within these subsets will involve a consideration of the sum of gauche interactions. These are unranked and can be more or less significant depending on the exact situation: (a) steric or size hindrance is always repulsive for two non-hydrogen groups that are gauche, (b) charge/charge (full or partial) can be repulsive (same charge) or attractive (opposite charge), and (c) intramolecular hydrogen bonds are attractive and stabilizing when there is a hydrogen bond donor that is gauche to a hydrogen bond acceptor (these same groups, if anti to each other, are too far apart to form a hydrogen bond).

Often, two or more of these gauche interactions are operating simultaneously. Sometimes, their effects reinforce each other, that is, both are destabilizing, and so the relative energies of a pair of conformations can be predicted reliably. For example, one of the two distinctive staggered conformations for 1,2-dibromoethane and 1,2-dichloroethane (Figure 0612) have a gauche interaction between the two bromine atom groups and the two chlorine atom groups, respectively.

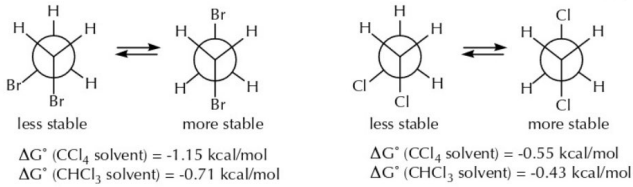

Figure 0612
Conformational energies for 1,2-dibromoethane and 1,2-dichloroethane.

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The two cases in Figure 0612 are comparable. In both cases, there are two gauche interactions and they are both destabilizing: steric hindrance and partial charge repulsion when the halogen atoms are in a gauche relationship. Because both of these gauche interactions are destabilizing, the anti form is anticipated to be the more stable conformation. The ΔG° measurements have been reported for both compounds in two different solvents, carbon tetrachloride (CCl_4) and chloroform ($CHCl_3$), and the negative values for these equilibria, as drawn, indicate that the anti conformation is consistently more stable than the gauche form.

The different values for the ΔG° measurements in the two different solvents is a great reminder that the experimental conditions under which a measurement is made plays a part in the observed outcome (*Heisenberg Uncertainty*: method and object are linked). These two solvents differ in polarity. Carbon tetrachloride has no molecular dipole moment and is less polar than chloroform, which has a permanent dipole moment. Notice the consistency in the two pairs of experimental results: The gauche conformation is disproportionately more stable in chloroform than it is in carbon tetrachloride (i.e., less difference in energy between the two forms).

When the two halogen atoms are anti, the conformation has no dipole moment because the two equal carbon-halogen bond dipoles are pointed in exactly the opposite direction and cancel each other out. In the gauche conformation, however, there would be a dipole moment. In the polar solvent ($CHCl_3$), the molecular dipole created by the gauche halogen atoms would be more stabilized by dipole-dipole attraction compared to the nonpolar solvent (CCl_4), where no such stabilization exists. Said another way, the nonpolar solvent does not stabilize the polar gauche form as much as the polar solvent does.

What is difficult to predict is how the 1,2-dibromoethane case will compare with the 1,2-dichloroethane case. Bromine atoms are larger than chlorine atoms, and so the steric repulsion would be predicted to be greater for bromine than chlorine (prediction: the anti bromine atoms are more stable than the anti chlorine atoms). On the other hand, the electronegativity difference between carbon and chlorine is greater than between carbon and bromine, and so the charge/charge repulsion would be predicted to be greater for chlorine than bromine (prediction: the anti chlorine atoms are more stable than the anti bromine atoms). The only way to resolve this conflict in predictions is through experiment. As given, the data are more consistent with the steric repulsion being more important than the charge repulsion. In fact, more sophisticated analyses exist, and we will consider that in a later chapter. For now, we will stick with the criteria provided in Figure 0611. *This result cannot be overgeneralized: It is not true that the steric effect will always outweigh the charge effect.*

Although the molecular structures are not that much more complex, the conformations for 1,2-ethanediol (Figure 0613) and some structurally related compounds present a more complicated problem for predicting relative energies.

1,2-ethanediol: The positive ΔG° measurement means that the gauche form is more stable than the anti form. The same gauche interactions described for the 1,2-dibromoethane and 1,2-dichloroethane would be anticipated here and would favor the anti form (steric interaction and charge/charge repulsion of the electronegative atoms). But for 1,2-ethanediol, there is a stabilizing gauche interaction that was not possible in the previous compounds: hydrogen bonding. One of the hydroxyl groups can serve as a hydrogen bond donor while the other can serve as a hydrogen bond acceptor. Although it cannot be predicted, the attractive effect of the hydrogen bonding must be overcoming the two repulsive effects and providing a net stabilization to the gauche conformation. The ΔG° values is the contribution of those three effects (steric, charge/charge, hydrogen bonding) acting together, *and as has been cautioned already, the result cannot be overgeneralized: It is not true that the hydrogen bond effect will always outweigh the other two effects.*

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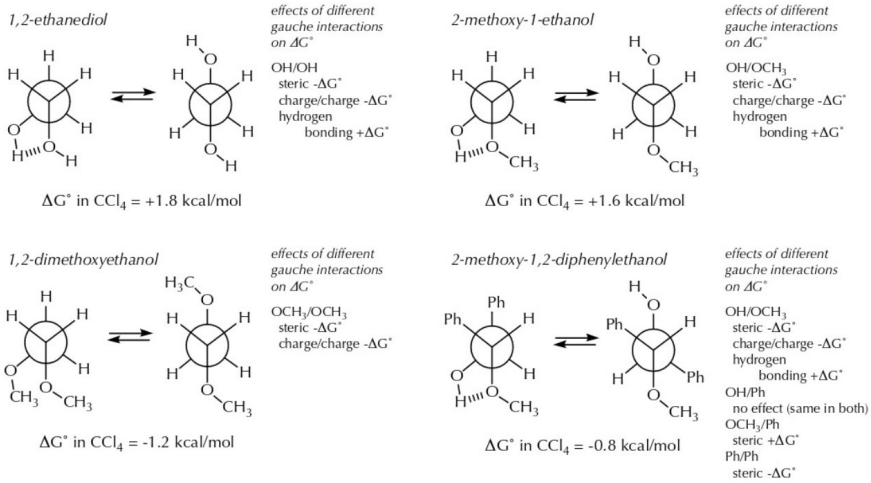
Figure 0613

Conformational energies for 1,2-ethanediol and related compounds.



2-methoxy-1-ethanol: In this molecule, one of the hydroxyl groups in ethanediol has been replaced by a methoxy group. The positive ΔG° measurement is nearly identical (+1.6 kcal/mol) to the ethanediol case (+1.8 kcal/mol), and the explanation is the same. The hydroxyl group is a hydrogen bond donor, and the oxygen atom of the methoxy group can be a hydrogen bond acceptor. The intramolecular hydrogen bond can only form when these two groups have a gauche relationship, and the net result is stabilization for that conformation.

1,2-dimethoxyethane: When both of the hydroxyl groups in ethanediol are replaced by methoxy groups, there is no longer a hydrogen bond donor in the molecule. This molecule is most comparable to the previous 1,2-dihaloethane examples, where the two possible gauche interactions (steric hindrance, charge/charge repulsion) are destabilizing, and the anti conformation is more stable than the gauche form. The negative ΔG° measurement is consistent with that prediction.

2-methoxy-1,2-diphenyl-1-ethanol: In this molecule, two benzene rings have added to the methxoyethanol structure. Now, there are additional gauche interactions to consider. Based upon the experimental result, the conformation without the intramolecular hydrogen bond is slightly more stable (0.8 kcal/mol) than either of the conformations where the hydrogen bond can form, illustrating that the presence of a possible hydrogen bond does not automatically make these conformations more stable. In this example, the forms with the intramolecular hydrogen bonds also create a steric gauche interaction between the two phenyl groups, and this destabilization must be enough to overcome the stabilization of the hydrogen bonds.

More guidance about examples such as this last one, with multiple competing factors, is discussed in the next section.

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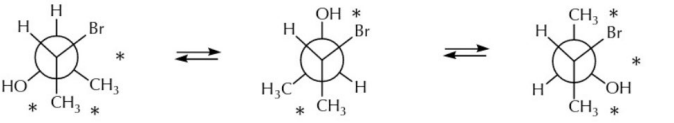
D. Balancing Competing Factors in Conformational Analysis

As demonstrated in the previous section, there is no absolute ranking of the different types of gauche interactions. Sometimes, as in the case of the 1,2-dibromoethane and 1,2-dichloroethane examples, the factors go in the same direction, and the more versus less stable conformation is predictable. But most of the time, the balance is not so easy to predict, and you either need the experimental data from comparable cases with which to make a prediction, or you need the experimental result from which you can make a conclusion.

In the next example, the experimental values for relative stabilities of this molecule are unknown, but the individual gauche interactions are known from a series of simpler molecules. For instance, the CH_3/CH_3 gauche interaction (0.9 kcal/mol) can be estimated from the butane case. Comparable data from other molecules gives the gauche interactions for CH_3/OH (0.3 kcal/mol), Br/CH_3 (0.2 kcal/mol), and Br/OH (1.5 kcal/mol). Using these values, estimates for the relative energies of the three conformations in Figure 0614 can be estimated.

Figure 0614

Three staggered conformations with multiple known gauche interactions (*).



$CH_3/OH + 0.3$ kcal/mol
$Br/CH_3 + 0.2$ kcal/mol
$CH_3/CH_3 + 0.9$ kcal/mol

+ 1.4 kcal/mol
most stable

$Br/OH + 1.5$ kcal/mol
$CH_3/CH_3 + 0.9$ kcal/mol

+ 2.4 kcal/mol
least stable

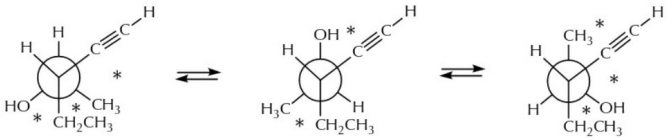
$CH_3/OH + 0.3$ kcal/mol
$Br/CH_3 + 0.2$ kcal/mol
$Br/OH + 1.5$ kcal/mol

+ 2.0 kcal/mol
intermediate stability

The situation is worse for the three conformations in Figure 0615: The experimental measurements are unknown for this compound and the individual pairwise comparisons are unknown.

Figure 0615

Three staggered conformations with multiple unknown gauche interactions (*).



There are only steric interactions to consider in this example because there is no hydrogen bond acceptor present for the hydroxyl group to interact with, and there are no possible charge/charge interactions. Without any other data, one strategy would be to count up the gauche interactions. The conformer in the center has two, while the other two conformations have three. And while there may well be quantitative differences in the magnitudes of the individual gauche interactions, we do not have those data and so we provide a qualified prediction: Based upon counting gauche steric interactions, and in the absence of other gauche interactions, the conformation in the center, with two gauche interactions, is predicted to be the more stable form. There are not enough data to make a reliable prediction about the relative stability of the other two conformations, as both of them have three gauche interactions.

Accurate or not, this would be the best prediction.

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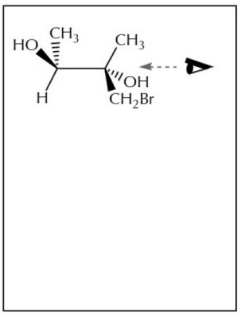
PRACTICE QUESTIONS

6.01 Provide the Newman projection for each of the indicated bonds, using the point of view implied by the eye.

(a)



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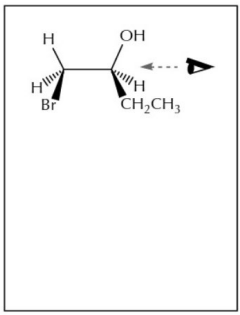

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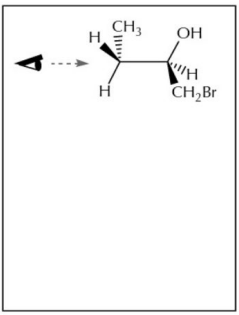

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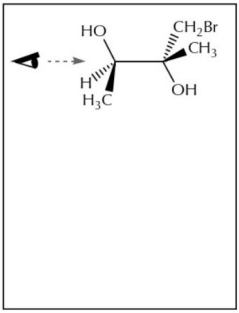
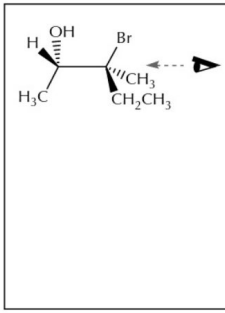
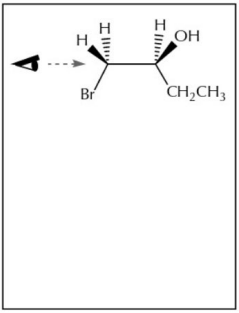


(e)



(f)



6.02 For each of the molecules in 6.01, provide the complete IUPAC name. For any molecules that are identical stereoisomers, tell whether their conformations are identical or different.

(a)

(b)

(c)

(d)

(e)

(f)

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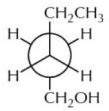
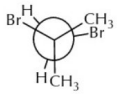
6.03 For each of the following, draw a Newman projection according to the directions for rotating the bond. Redraw the conformation of your resulting Newman projection using a 3D (line/dash/wedge) representation. Be sure to include the "eye" that tells what the viewing orientation applies to your 3D drawing.

(a)



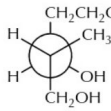
rotate the **back** atom **clockwise** by 120°

(b)



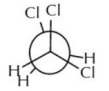
rotate the **back** atom **clockwise** by 180°

(c)



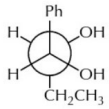
rotate the **front** atom **counterclockwise** by 120°

(d)



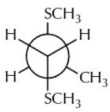
rotate the **back** atom **counterclockwise** by 60°

(e)



rotate the **back** atom **clockwise** by 180°

(f)



rotate the **front** atom **clockwise** by 120°

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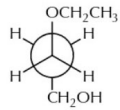
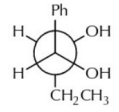
6.04 For each of the following, tell how many gauche interactions are present, and list the type of interaction associated with each of them (steric repulsion, charge/charge repulsion, charge/charge attraction, and/or hydrogen bonding).

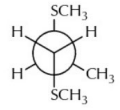
(a)



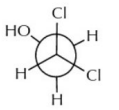
(b)



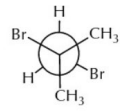
(c)



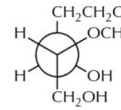
(d)



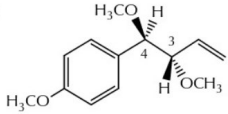
(e)



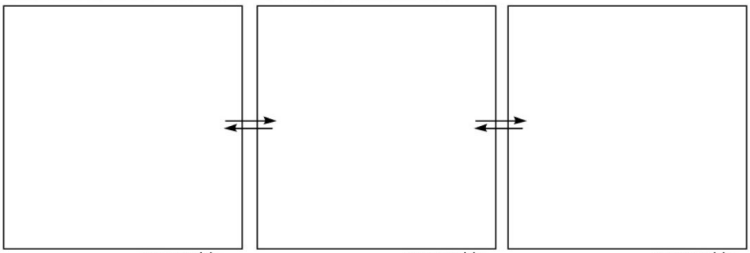
(f)



6.05 Cytokines are small proteins that are released by cells for the purpose of communication. Cytokine inhibitors slow or prevent the normal biological action of cytokines. The following molecule was prepared during the synthesis of a cytokine inhibitor called cytoxazone A. Starting with this structure, draw the Newman projections for the three staggered conformations of cytoxazone A using C3 as the front atom and C4 as the back atom. Draw the conformation shown in the first space, then turn the front carbon *in a clockwise direction* to create the other two staggered forms. Rank the relative stabilities of these three conformations.



cytoxazone A



this conformation: most stable / least stable / intermediate stability

this conformation: most stable / least stable / intermediate stability

this conformation: most stable / least stable / intermediate stability

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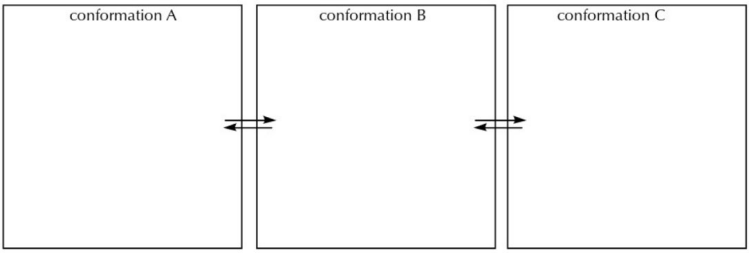
6.06 (*S*)-2-Bromo-3-methylbutane is a commonly used reagent in organic synthesis. Provide a conformational analysis for the C2-C3 bond of this compound.

(a) Draw the Newman projections for the three staggered conformations (C2 as the front atom).



(b) Given the information in the following data table, draw the conformational energy diagram starting with conformation A and ending with conformation C, from part (a).

Data Table:	gauche interaction:	CH_3/CH_3 = 0.9 kcal/mol	CH_3/Br = 0.2 kcal/mol
	eclipsed interaction:	CH_3/H = 1.7 kcal/mol CH_3/Br = 1.8 kcal/mol	CH_3/CH_3 = 2.5 kcal/mol H/Br = 0.8 kcal/mol

6.07 The conformational analysis for the C1-C2 bond of 1-bromobutane results in two conformations that each have a single gauche interaction. Using standard 3D (line/dash/wedge) notation (not Newman projections), draw one of the conformations for the C1-C2 bond of 1-bromobutane that has a gauche interaction. Then draw the other conformation with a gauche interaction as well as the eclipsed for that is predicted to exist when these two forms interconvert.

3D drawing for C1-C2 bond of 1-bromobutane that has a gauche interaction

3D drawing for C1-C2 bond of 1-bromobutane (eclipsed form during the interconversion of the two gauche forms)

3D drawing for C1-C2 bond of 1-bromobutane that has a gauche interaction, continuing from the first drawing through the eclipsed form

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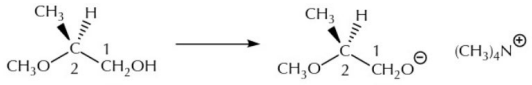
6.08 2-Methoxy-1-propanol (compound P) is used in the manufacture of surface coatings, varnishes, paints, and agricultural pesticides, as well as a solvent for various types of inks. With a pK_a of about 16, compound P can be deprotonated to give its conjugate base (the ionic compound Q, shown here with the tetramethylammonium, $(CH_3)_4N^+$ cation).



compound P compound Q

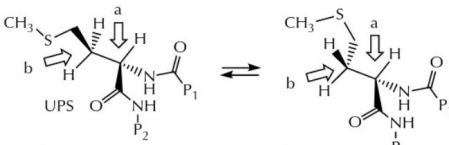
The most stable conformations for these two, as viewed along the C1-C2 bond, have a different relationship between the two oxygen atom containing groups.

(a) Using a Newman projection, provide a drawing for the most stable conformation of compound P, as viewed down the C1-C2 bond (see figure for labels) and with C1 as the front atom and C2 in the back.

(b) Using a Newman projection, provide a drawing for the most stable conformation of compound Q, also as viewed down the C1-C2 bond (see figure for labels) and with C1 as the front atom and C2 in the back.

(c) What is the reason why the more stable conformation for compound P is different from compound Q?

6.09 The ubiquitin/proteasome system (UPS) is a major protein degradation pathway in eukaryotes. Molecules that can inhibit unwanted degredation are attractive targets for autoimmune disorders. In one such study, an inhibitor molecule is proposed to make the following conformational change in the UPS.



Conformation L1 Conformation L2

"P_1" and "P_2" refer to different protein units, which are sp^3 carbon atoms at the "P" positions.

gauche interaction
P_1 unit/-CH_2SCH_3 (0.5 kcal /mol)
P_2 unit/-CH_2SCH_3 (1.1 kcal /mol)

(a) Draw the two Newman projections for these conformations. Use the point of view where the carbon a is the front atom and carbon b is the back atom (see above for labels).

Conformation L1 Conformation L2

(b) As drawn in (a), what is the value of the ΔG° for this conformational change?

kcal/mol

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6.2 Partial Bond Rotations in Small Rings

A. Cyclopropane

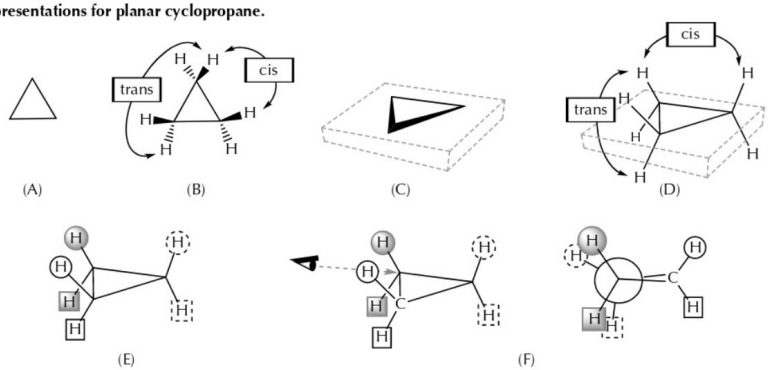
The three-membered ring of cyclopropane is planar, by definition, as three points (atoms) define a plane. The molecule is stable but experiences strain energy because each of the tetravalent carbon atoms have two of their bonds pulled together to make a 60° angle compared with the ideal tetrahedral value of 109.5°.

The three carbon-carbon bonds in cyclopropane are fixed into a planar geometry and cannot rotate at all. Consequently, all six of the appended hydrogen atoms are also fixed in space and unable to move with respect to each other. The entire molecule is more or less locked into a single conformation and has no other possible significant movements beyond the normal bending and vibrations that take place in molecules.

The drawings used to represent cyclic molecules vary from compound to compound, and as always, the drawing selected for use depends on what is being communicated about the structure. A few different drawings for cyclopropane are presented in Figure 0616. Illustration (A) is the typical line abbreviation formula, while (B) adds in the pairs of hydrogen atoms at each vertex. With the ring bonds shown in the plane of the writing surface, the distorted tetrahedra would show one of the bonding sites pointed towards the viewer (wedge) and the other pointed away (dash).

Figure 0616

Representations for planar cyclopropane.



Illustrations (A) and (B): The perimeter of a ring is a common point of reference because the carbon-carbon bonds cannot rotate. Drawn as in (A) and (B), the imagined surface of the ring facing the viewer is called its top face, while the underside, with respect to this drawing, is called its bottom face. The three hydrogen atom groups directed towards the viewer, in this drawing, are gathered along the top face of the ring. The relative same-sidedness of these three groups is described using the term "cis," just as it was in describing the relationship of two groups on the same side of a double bond. The three hydrogen atoms gathered along the bottom face of the ring, as drawn, are also relatively cis to one another. While two hydrogen atoms on the same carbon do not have any special geometrical term to describe their relationship, two groups on different faces and at different vertices are said to have a "trans" relationship. Grab ahold of any of the hydrogen atoms in cyclopropane and it has two other hydrogen atoms in the structure to which it is cis, located at different vertices and on the same face, and two that are trans, located at different vertices and on the opposite face.

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Illustration (C): The plane of the ring is drawn in a pseudo-perspective. The intent is to show what a triangular shape would look like if it were lying face down on a table that you were standing above and looking down at from a high angle. In (C), the wedged lines are used to try and give a few more spatial cues for the drawing. As represented, it is as though the triangular shape was propped up on one of its sides and then fell forward, and now has that top vertex pointed at you.

Illustration (D): As in (B), there is a hydrogen atom group pointed above the plane of the ring at each vertex, and also one below. If you now imagine that triangular object falling forward onto a tabletop, then three of the bonding sites, with their hydrogen atoms, will be directed upwardly, while the other three will be directed downwardly. At the front vertex, closest to you, the upwardly directed bond sits in front of the back bond of the ring, from your viewpoint. A standard drawing convention used to better convey the three-dimensional spatial cue is to put a break in the line that sits behind your point of view. The placement of the six hydrogen atoms and their bonds is illustrated in (D). The three that are "up" are all cis to each other; the three that are "down" are all cis to each other; and grabbing any one of the hydrogens defines the two on its opposite side, on the other two atoms of the ring, as trans.

Illustration (E): The hydrogen atoms have been highlighted. The three on the top face are outlined with circles, while the three on the bottom face are outlined with squares. The open shapes are in the front, with respect to the viewer, and both projected towards the viewer, while the fully shaded and dotted line shapes are attached to one of the carbon atoms along the back edge.

Illustration (F): By defining the point of view shown on the left, in (F), a Newman projection for cyclopropane can be drawn. Because of the planar structure, the carbon-carbon bonds are fixed into an eclipsed form, and so is any pair of adjacent carbon-hydrogen bonds.

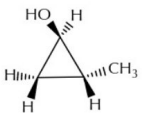
The drawings in Figure 0616 are foundational. The perspective drawings (e.g., (D)) are intended to convey the spatial relationships you might see in a physical model (yet another reminder for you to get models and to ensure you see, in your mind's eye, the spatial relationships that are coded into these drawings). This set of drawings can not only be used as templates for 3D illustrations of other three-membered rings, but the principles used in these visualizations can be extrapolated to rings of any size.

The rest of this section draws upon your prior understanding of stereoisomerism.

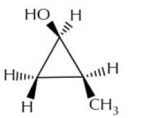
Figure 0617 provides drawings of the four stereoisomers for 2-methyl-1-cyclopropanol. Translating any of these drawings into the pseudoperspective views used in Figure 0616 is an important skill. Just as when you draw a tetrahedron with line/dash/wedge notation, there are many different equally correct translations for any of the 2-methyl-1-cyclopropanol stereoisomers. There is no rule governing how to represent the translated structure beyond making sure that you have actually represented the molecule you intend to redraw.

Figure 0617

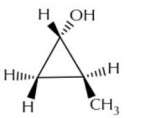
Stereoisomers of 2-methyl-1-cyclopropanol.



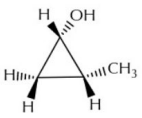
(1*R*, 2*R*)-2-methylcyclopropane



(1*R*, 2*S*)-2-methylcyclopropane



(1*S*, 2*R*)-2-methylcyclopropane



(1*S*, 2*S*)-2-methylcyclopropane

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In Figure 0618, a possible stepwise process for translating the (1*R*, 2*S*)-stereoisomer is presented. The process shown in Figure 0618:

Step 1. Draw the ring in its pseudo-perspective form.

Step 2. Select the vertex on the line/dash/wedge drawing you will place first (the one with the OH).

Step 3. Identify the vertex on the pseudo-perspective drawing that you want to use as one selected in Step 2 (it does not matter which one).

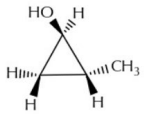
Step 4. Make the easy decision: the upwardly directed bonding site on the line/dash/wedge drawing (the one with the OH) is the one pointed upwardly at the vertex you selected in Step 3 (draw in the OH up and the H down)

Step 5. Be internally consistent: starting from the upwardly pointed OH in the line/dash/wedge drawing, you move clockwise around the perimeter of the ring by one atom to get to the vertex with the methyl group, and it is pointed downwardly; so this is exactly what you need to translate onto the other drawing: start with the OH up and move clockwise to the next atom.

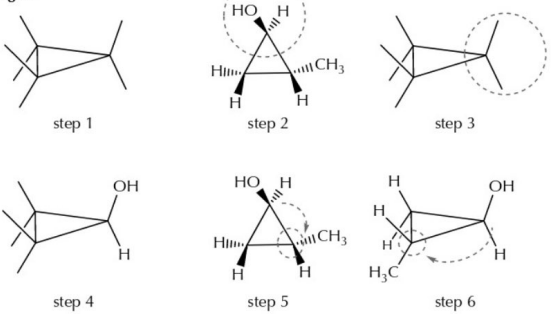
Step 6. The methyl is directed downwardly, in the same direction as the OH. Add the last Hs.

Figure 0618

Translating a line/dash/wedge drawing of (1*R*, 2*S*)-2-methyl-1-cyclopropanol.



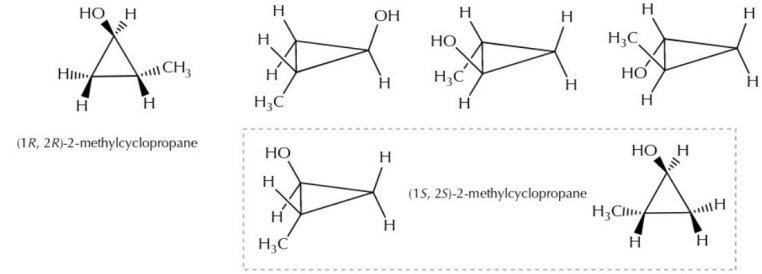
(1*R*, 2*R*)-2-methylcyclopropane



A few more drawings for the (*1R, 2S*)- 2-methyl-1-cyclopropanol are given in Figure 0619. If you are inconsistent in the translation, you could easily draw the enantiomer by mistake (one example of that is also shown).

Figure 0619

A few other 3D drawings for (1*R*, 2*S*)-2-methyl-1-cyclopropanol.



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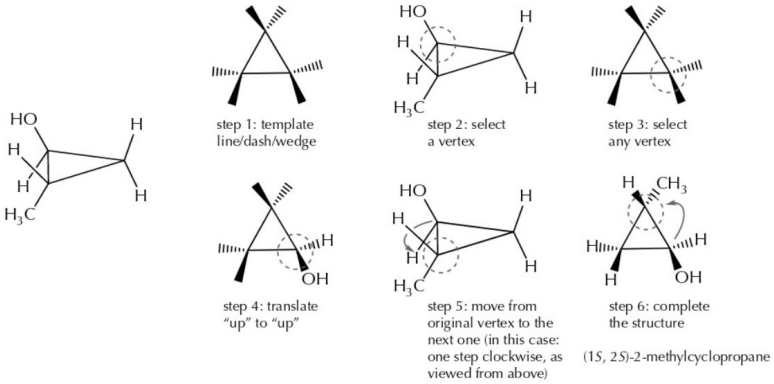
Being able to read all of these drawings and assign the "R" and "S" configurations can be challenging, and so accurately and rapidly translating them into equivalent drawings is an exceptionally useful skill and worthy of as much practice as it takes to get it right. In Figure 0620, the pseudoperspective form of the (1*S*, 2*S*)-2-methyl-1-cyclopropanol from Figure 0619 is the starting point for a translation to the line/dash/wedge form, where assigning the stereochemical labels is generally easier to do.

Figure 0620

Translating into a line/dash/wedge drawing to assign "R" and "S" labels.


step 1: template line/dash/wedge
step 2: select a vertex
step 3: select any vertex
step 4: translate "up" to "up"
step 5: move from original vertex to the next one (in this case: one step clockwise, as viewed from above)
step 6: complete the structure
(1S, 2S)-2-methylcyclopropane

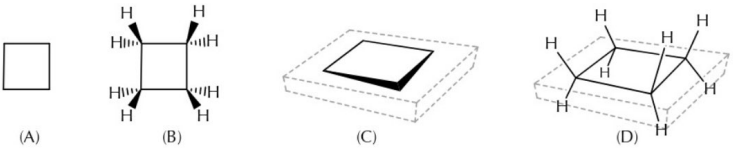
B. Cyclobutane

The drawing principles illustrated for cyclopropane are equally valid for all ring sizes. Every different ring has its own set of pseudoperspective drawings that chemists have developed over time.

Figure 0621 follows directly from Figure 0616. Planar cyclobutane has a slightly less strained ring angle (90° rather than 60°, and closer to the unstrained tetrahedral value). The ring has two faces, each with four bonding sites that are all mutually cis to one another, as well as the trans relationship between groups on different vertices that are on opposite faces. The pseudoperspective drawing for cyclobutane can be shown in a planar form and, as in the cyclopropane case, all of the adjacent bonding sites on the same face would be eclipsing each other. The translation of specific molecules from line/dash/wedge to pseudo-perspective also follows directly from the cyclopropane case.

Figure 0621

Representations for planar cyclobutane.



An important difference between cyclopropane and all other saturated rings is that only cyclopropane is restricted to a planar shape. In the planar form, the bonds around the perimeter of the ring are eclipsing

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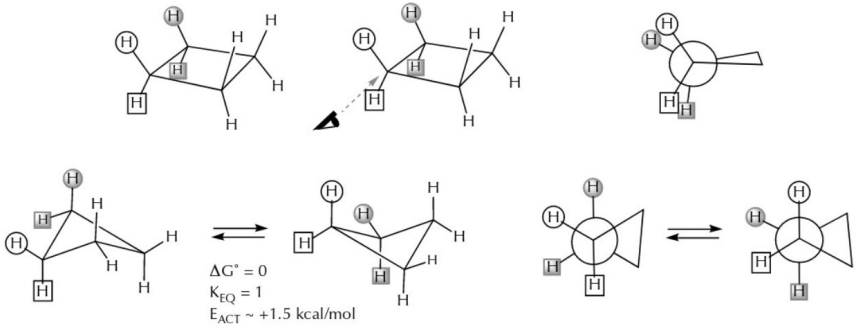
one another. Starting with cyclobutane, the rings atoms are more flexible. Although a full bond rotation is not possible, a partial bond rotation can relieve the repulsive effect caused by the eclipsed bonds.

Figure 0622 uses the same Newman projection strategy for cyclobutane that was used earlier with cyclopropane in Figure 0616. All of the carbon-carbon bonds in cyclobutane can undergo a partial bond rotation. This partial bond rotation moves the carbon-hydrogen bonds away from eclipsing, relieving that interaction from the planar form. Experimentally, the more stable form of cyclobutane is when it is slightly folded along one of its diagonals. Two opposite vertices can either be folded upwardly or folded downwardly.

Figure 0622

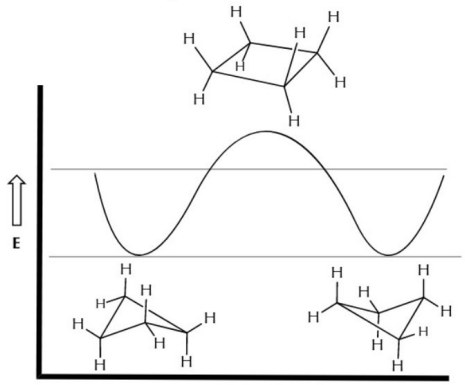
Newman projections used to illustrate partial bond rotation in cyclobutane.



In cyclobutane, the two folded conformations are equivalent, and so the equilibrium constant for the interconversion between them is 1 (Figure 0623). The planar form, containing the eclipsed bonds, is the high-energy transition state conformation, quite comparable to the way the eclipsed conformations of ethane and butane are the transition states between their staggered conformations. The more stable, bent geometries for the cyclobutane molecules are called the butterfly conformations.

Figure 0623

Energy diagram for the butterfly conformation interconversion of cyclobutane.



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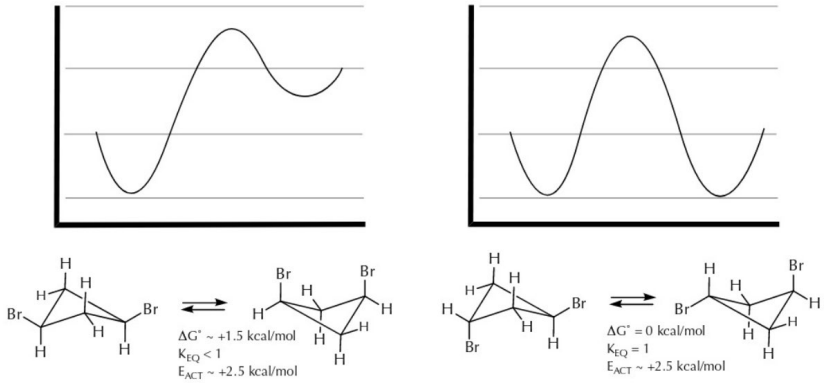
When there are substituent groups on a cyclobutane, the two butterfly conformations can end up having different stabilities based on all of the same criteria that were used to evaluate gauche interactions: steric repulsion, charge/charge attraction or repulsion, and hydrogen bonded attraction.

1,3-Dibromocyclobutane is an even-numbered ring with substituents at its opposite vertices, so there are two achiral stereoisomers: the *cis* and *trans* diastereomers. The two butterfly conformations for both stereoisomers can be drawn (Figure 0624). In *cis*-1,3-dibromocyclobutane, the two bromine atoms are pointed away from one another in one of the butterfly conformations (more stable), but they are nearly parallel in the other, where there would be a greater effect from both steric interference and an unfavorable partial charge repulsion between the two electronegative atoms (less stable). For *trans*-1,3-dibromocyclobutane, the two conformations are identical and equal in stability.

Figure 0624

Conformational energy diagrams for *cis*- and *trans*-1,3-dibromocyclobutane.



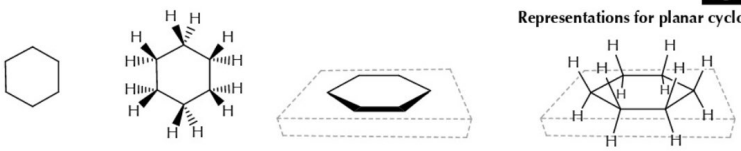
C. Cyclohexane

As the size of a ring increases, the angle strain is less severe than in the 3- and 4-membered rings because the molecule is more flexible. It is easier for the bonds in the ring to undergo partial rotations to alleviate the increasing number of eclipsing interactions that would exist in a planar conformation.

Figure 0625 shows different representations for cyclohexane, following the pattern used for illustrating cyclopropane (Figure 0616) and cyclobutane (Figure 0621). If cyclohexane had a planar ring, the bond angle would be 120° and the two sets of six carbon-hydrogen bonds along the top and bottom faces would be eclipsed around the perimeter. The pseudoperspective drawing for cyclohexane can be shown in a planar form and, as in the previous cases, translating this representation into a line/dash/wedge drawing and/or a Newman projection (for any defined bond) can be shown. This is not a stable conformation for cyclohexane.

Figure 0625

Representations for planar cyclohexane.



(A) (B) (C) (D)

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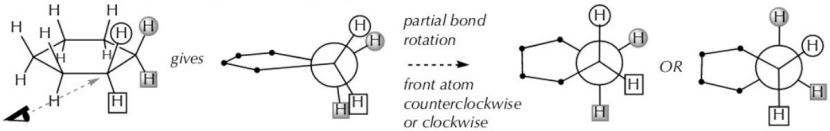
Experimentally, the cyclohexane ring is well studied. Six-membered rings occur naturally in many different organic compounds. Some facts that are known about the cyclohexane structure include:

(a) it does not exhibit any ring strain
(b) its carbon atoms are nearly perfectly tetrahedral
(c) the conformational arrangement for any of its six C-C bonds is staggered
(d) the six C-H bonds along the top face are organized into two sets of three
(e) the six C-H bonds along the bottom face are organized into two sets of three

Using the Newman projection of one of the carbon-carbon bonds in the less stable planar form as a starting point, the carbon-carbon bond can undergo a partial bond rotation, in one direction or the other, which relieves the eclipsing interactions and puts the bond into a staggered conformation (Figure 0626).

Figure 0626

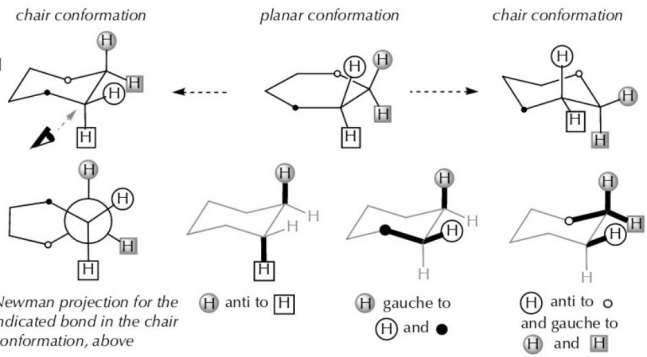
Partial bond rotation gives staggered bonding in cyclohexane conformations.



The partial bond rotation shown in Figure 0626 happens at each bond in the cyclohexane ring, and the resulting conformation is a molecular geometry where all five of the criteria listed above are true. A pseudoperspective drawing for planar cyclohexane is shown in the center of Figure 0627 with the same four hydrogen atoms highlighted as in Figure 0626. The pseudoperspective drawings for the partial bond rotations that move the bonds into more stable staggered conformations for the entire molecule are shown to the left and right of the less stable planar form. These pseudoperspective drawings represent what are called the two chair conformations of cyclohexane. The anti and gauche relationships that can be seen easily in the Newman projection can also be visualized in the chair conformation drawings. A few of these relationships are illustrated in Figure 0627.

Figure 0627

Newman projections illustrate the staggered bonding in chair cyclohexane conformations.


chair conformation
planar conformation
chair conformation
Newman projection for the indicated bond in the chair conformation, above
H anti to H
H gauche to H and ●
H anti to ○ and gauche to H and H

Molecular models are once again exceptionally useful for understanding the relationships within the three-dimensional structure and how they are represented in the two-dimensional drawings. The next topic is singularly devoted to how to place and interpret the 18 lines that are used to properly draw the chair conformation of cyclohexane.

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Including all of the atoms, there are 18 bonds in a molecule of cyclohexane: 6 carbon-carbon bonds and 12 carbon-hydrogen bonds. The molecular geometry for all 18 bonds can be shown explicitly in pseudo-perspective drawings for both of the possible chair conformations. A summary of the relationships of the bonds that define the chair conformation of cyclohexane are listed here and illustrated in Figure 0628.

(A) There are three pairs of parallel carbon-carbon bonds in the ring, arranged in a regular zig-zag pattern around the perimeter; the central pair of lines in the drawing are mutually parallel at about +/- 45° and are directly above and below each other at about the distance corresponding to the bond length that you draw.

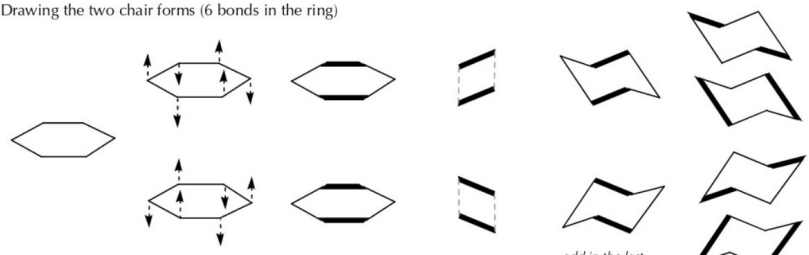
(B) Six of the carbon-hydrogen bonds are mutually parallel, and also parallel to an imaginary axis that is perpendicular to the ring; there is one of these at each vertex, and they alternate up-down (top face/bottom face, trans), pointing in the same direction as the vertex. These are called the axial bonding sites.

(C) Six of the carbon-hydrogen bonds are arrayed along the equator of the molecule, one at each vertex pointing out from the center; they are also alternating relatively up and down at their respective vertices (top face/bottom face, trans), parallel to each other on opposite ends of the ring and parallel to the carbon-carbon bonds described by the other four carbons. These are called the equatorial bonding sites; the three drawn on the left-hand side of the structure point to the left, and the three on the right point to the right.

Figure 0628

Stepwise construction of the two chair cyclohexane conformations.

Drawing the two chair forms (6 bonds in the ring)


starting with the pseudo-perspective planar form
alternating vertices move up and down in one of two patterns
focus on the two "central" bonds in the drawing
slant them +45° or -45° and keep them parallel
add in the last two vertices, and note the zig-zag (up-down) pattern that creates two more pairs of parallel lines in each of the drawings

Add in 6 axial bonding sites alternate straight up and down, all parallel, and according to the direction of the vertex

Add in 6 equatorial bonding sites, three pointed left and three pointed right, parallel to the ring bond one atom away

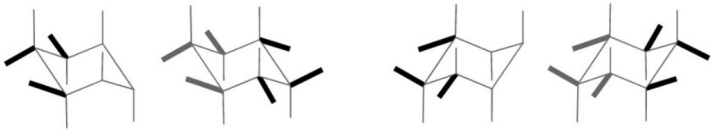


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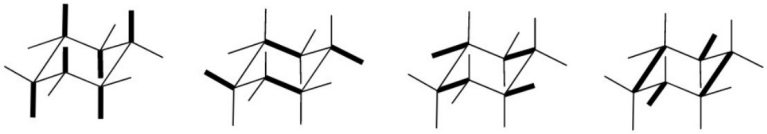
Figure 0628

(continued from previous page)

SUMMARY:

Highlighting the sets of parallel line relationships in a cyclohexane chair conformation drawing:



6 axial bonding sites all mutually parallel (3 up, 3 down)

2 equatorial bonding sites (1 pointed left and 1 right) parallel to 2 ring bonds

2 equatorial bonding sites (1 pointed left and 1 right) parallel to 2 ring bonds

2 equatorial bonding sites (1 pointed left and 1 right) parallel to 2 ring bonds

The two chair conformations of cyclohexane are equal in stability, so the equilibrium constant for the interconversion between these two forms equals 1 (50:50 distribution). The transformation between the two forms takes place readily at room temperature, with an activation energy of 10.8 kcal/mol that allows them to interconvert at a rate of about 100,000 times per second. The change from one chair form to another is not a smooth, single step, because a one-step pathway involving the fully planar form has a higher activation energy than the multistep pathway. As illustrated in Figure 0629, a relatively lower activation energy occurs when only half of the chair flattens out into a planar form through a transition state called a half-chair. The motion that flattened that half of the chair continues, and a quite flexible twist form is proposed to result.

With a good set of molecular models, you can generally tell that the chair form is somewhat rigid while the twist form can wiggle around from one twist form to another. The transition state between the twist conformations is called a boat conformation. Ultimately, the other side of the original ring flattens out, resulting in the other chair conformation.

The actual geometry and bonding relationships in the chair cyclohexane conformation are poorly represented in the literal reading of the two-dimensional drawing. You will spend more time than you need to, and probably never truly appreciate the structure, if you stubbornly refuse to simply get a set of models to build and inspect the structure and to consider its geometry relative to the drawings. *Hours of wasting time with text, video, or other fundamentally two-dimensional presentations can be avoided in minutes with a model.*

The correspondence between the atoms and the bonding sites in the two chair forms is another feature of this conformational analysis. As shown in Figure 0630, the left- and right-most vertices, as drawn, remain the same in the two chair forms. The sense of the pseudoperspective also remains the same, and so the lower edge (filled circles) of the ring, as drawn, remains closer to the viewer.

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Figure 0629

Energy diagram for the chair-to-chair interconversion of cyclohexane.

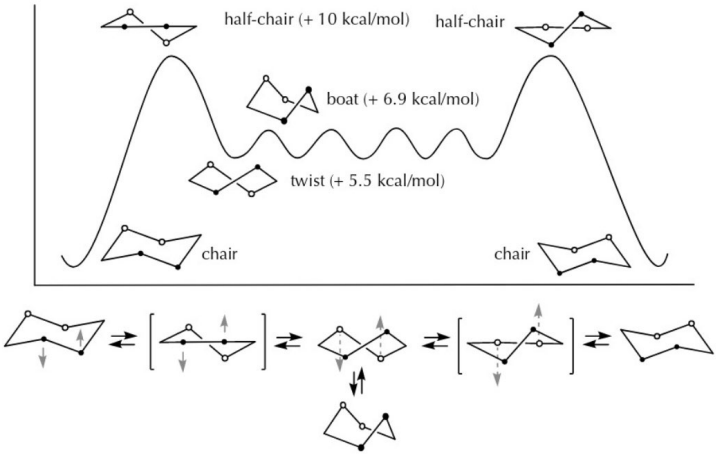
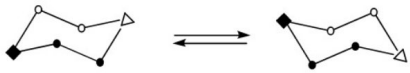


Figure 0630

Left-to-right and front-to-back correspondence in the two cyclohexane chair conformations.



The partial bond rotation that interconverts one chair form to the other also moves all of the axial bonding sites into corresponding equatorial positions, and all of the equatorial bonding sites into axial positions. A labeled set of atoms on the chair forms is shown in Figure 0631 for one of the carbon-carbon bonds, along with the corresponding Newman projections, to illustrate the changes. Figure 0632 shows the same interconversion, but this time with all of the axial positions in one conformation related to the equatorial positions that they occupy in the other.

Figure 0631

Axial to equatorial interconversion in the two cyclohexane chair conformations (highlighting one bond and its Newman projection).

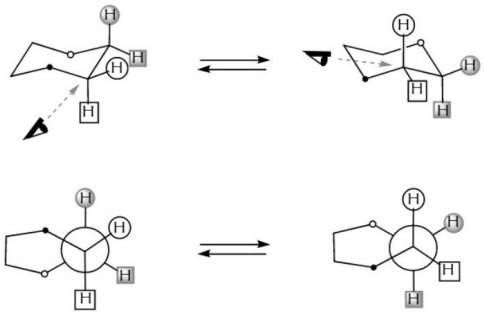


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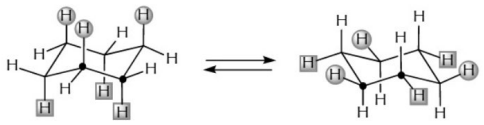
Figure 0632

Axial to equatorial interconversion in the two cyclohexane chair conformations (highlighting all of the changes)

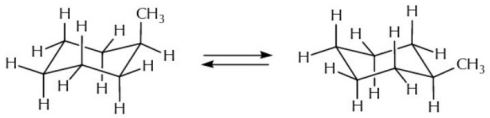


D. Substituted Cyclohexanes

Experimentally, there are two chair conformations for methylcyclohexane, and the reported energy difference ranges from 1.7–1.8 kcal/mol. Based upon the interconversion of axial and equatorial bonding sites that takes place in the two chair forms (Figure 0632), one of the two chair conformations for methylcyclohexane will have its methyl group in the axial position, and the other will have it in the equatorial position. These two conformations are shown in Figure 0633, along with the information that the conformation with the equatorial methyl group is more stable than the one with the axial methyl group.

Figure 0633

The two chair conformations for methylcyclohexane differ in stability.

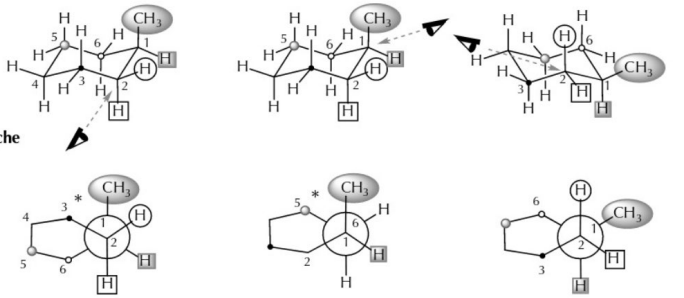


The explanation for this observed difference in stability can be revealed by looking at the Newman projections for the two bonds that include the atom with the methyl group. First, recall that all of the bonds in the cyclohexane ring are staggered, and so the same relationships used in the conformational analysis of butane and the other acyclic molecules can be applied here, namely, gauche interactions that involve steric hindrance, charge/charge interactions, and hydrogen bonding. A methyl group only has a steric effect.

One of the chair conformations of methylcyclohexane holds the methyl group in an axial position. The Newman projection for the C_1-C_2 ring bond from this conformation, which includes that methyl group, shows that it has a gauche steric interaction with the carbon atom of the ring that is two atoms away (C_3) from where it is bonded (Figure 0634). Similarly, when the Newman projection for the symmetrically positioned C_1-C_6 bond is drawn, the C_5 carbon has a gauche steric interaction with the methyl group.

Figure 0634

An axial substituent experiences two gauche interactions with the ring atoms.



axial methyl group
Newman projection for the C_1-C_2 bond (C_2 in the front)
* = gauche interaction

axial methyl group
Newman projection for the C_1-C_6 bond (C_1 in the front)
* = gauche interaction

equatorial methyl group
Newman projection for the C_1-C_2 bond (C_2 in the front)

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In the other chair conformation, the methyl group is in an equatorial position. The Newman projections for the C_1-C_2 and C_1-C_6 bonds are equally informative here, too. For both bonds, the equatorial methyl group is no longer gauche to C_3 and C_5, but rather it is anti to both of them.

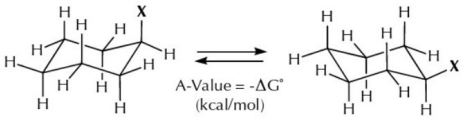
The conclusion here is completely generalizable: A chair cyclohexane conformation with a substituent group in the axial position experiences two gauche interactions with the ring atoms located two positions away from itself. If the interaction is only steric (repulsive), then the conformation with the group in the axial position is less stable than the one with the group in the equatorial position, where the substituent group is anti to the same ring atoms it was gauche to while in the axial position.

For methylcyclohexane, the conformation with the methyl group in the axial position is +1.7–1.8 kcal/mol less stable than the conformation with the methyl group in the equatorial position. This value is quite satisfyingly twice the value of +0.9 kcal/mol for the single methyl/methyl gauche interaction observed in butane (Figure 0608).

The difference in chair conformational energies for many different monosubstituted cyclohexanes has been measured, and the magnitude of the values correlates strongly with the anticipated extent of the gauche interaction. A table of experimentally determined values is given in Figure 0635 (the values are averages from multiple sources as different experiments can give different values). These $-\Delta G^\circ$ values, by convention, refer to the energy difference in going from the conformation with the substituent group in the axial position to the conformation with it in the equatorial position. These energy differences are called A-Values.

Figure 0635

Experimental A-Values for equatorial versus axial substituents on cyclohexane.



Group (X)		Group (X)		Group (X)	
CH_3	1.7	NH_2	1.25	OH	0.87
CH_2CH_3	1.75	$NH(CH_3)$	1.0	OCH_3	0.67
$C{\equiv}CH$	0.41	$N(CH_3)_2$	2.1	OCH_2CH_3	0.9
$HC{=}CH_2$	1.35	$NH_3^{\oplus}$	1.9	O_2CCH_3	0.6
$C{\equiv}N$	0.17	NO_2	1.1	O_2CH	0.3
$CH(CH_3)_2$	2.15	N_3	0.62	OSO_2CH_3	0.56
$C(CH_3)_3$	>4.5	NC	0.20	OSO_2tolyl	0.50
CH_2Ph	1.81	N=C=O	0.51	ONO_2	0.59
Ph	3.0	O=C-OH	1.35	$OSi(CH_3)_3$	0.74
F	0.15	$O{=}C{-}O^{\ominus}$	1.92	SH	1.2
Cl	0.48	$O{=}C{-}OCH_3$	1.29	SCH_3	0.9
Br	0.43	O=C-H	0.8	SPh	0.8
I	0.46	$O{=}C{-}CH_3$	1.17	SO_2Ph	2.5

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A few things of note when using the A-Values presented in Figure 0635 for an analysis:

(A) These values derive from mono-substituted cyclohexanes, and the energy differences represent steric effects only, as the ring does not have any other atoms with significant partial charge, charge, or hydrogen-bond donor/acceptor properties.

(B) A methyl group is a tetrahedral array of atoms; as its three hydrogen atoms are replaced by hydrocarbon groups (ethyl, isopropyl, tert-butyl) it becomes harder to impossible for the carbon chain in the axial position to turn away from the ring, and so the steric hindrance increases substantially.

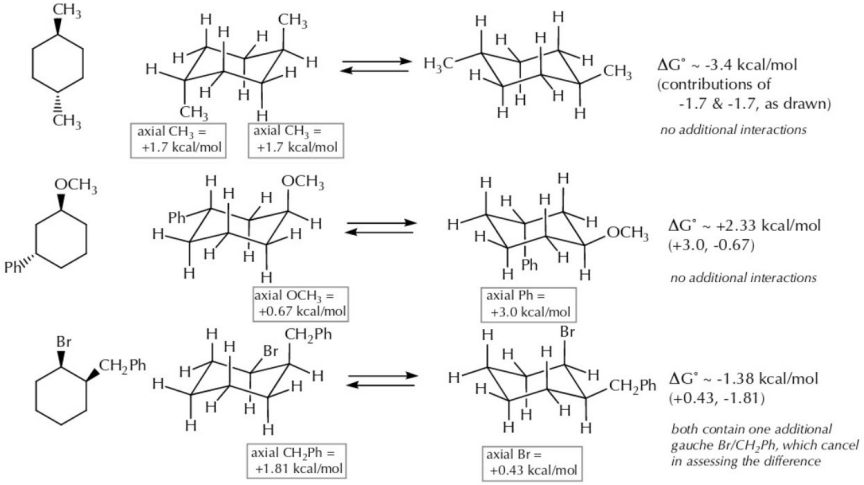
(C) Electronegative atoms with nonbonding electron pairs do not have a tetrahedral array of atoms (OH, OR, NH_2, Cl, Br) and so the gauche interaction is less severe; note that the steric effect does not increase substantially when the atoms are in different rows (OH versus SH, Cl versus Br): Although you might think the larger atom would show more hindrance, it also sits farther from the ring thanks to its longer bond distance.

(D) trigonal planer (C=C, C=O) and linear (CN) can have less steric interactions with the ring than tetrahedral carbon atoms, and so the steric hindrance for those groups is also generally less than for methyl and other tetrahedral carbon atoms.

When two or more groups are attached to a cyclohexane ring, the conformational analysis can sometimes be derived from the A-Values alone, and in other cases more experimental information is required. The key feature is whether or not the substituent groups have different interactions with one another in the two different chair conformations or not. If they do not, then the position of the equilibrium and the energy difference can be predicted quite reliably from the A-Values (Figure 0636). Care needs to be taken when you start from a planar representation, that you have translated the correct stereoisomer when there are stereocenters in the molecule. For this reason, the planar representation is included in both this figure and the next one.

Figure 0636

Some disubstituted cyclohexanes where A-Values can be used reliably.


axial CH3 = +1.7 kcal/mol
axial CH3 = +1.7 kcal/mol
ΔG° ~ -3.4 kcal/mol (contributions of -1.7 & -1.7, as drawn)
no additional interactions
axial OCH3 = +0.67 kcal/mol
axial Ph = +3.0 kcal/mol
ΔG° ~ +2.33 kcal/mol (+3.0, -0.67)
no additional interactions
axial CH2Ph = +1.81 kcal/mol
axial Br = +0.43 kcal/mol
ΔG° ~ -1.38 kcal/mol (+0.43, -1.81)
both contain one additional gauche Br/CH2Ph, which cancel in assessing the difference

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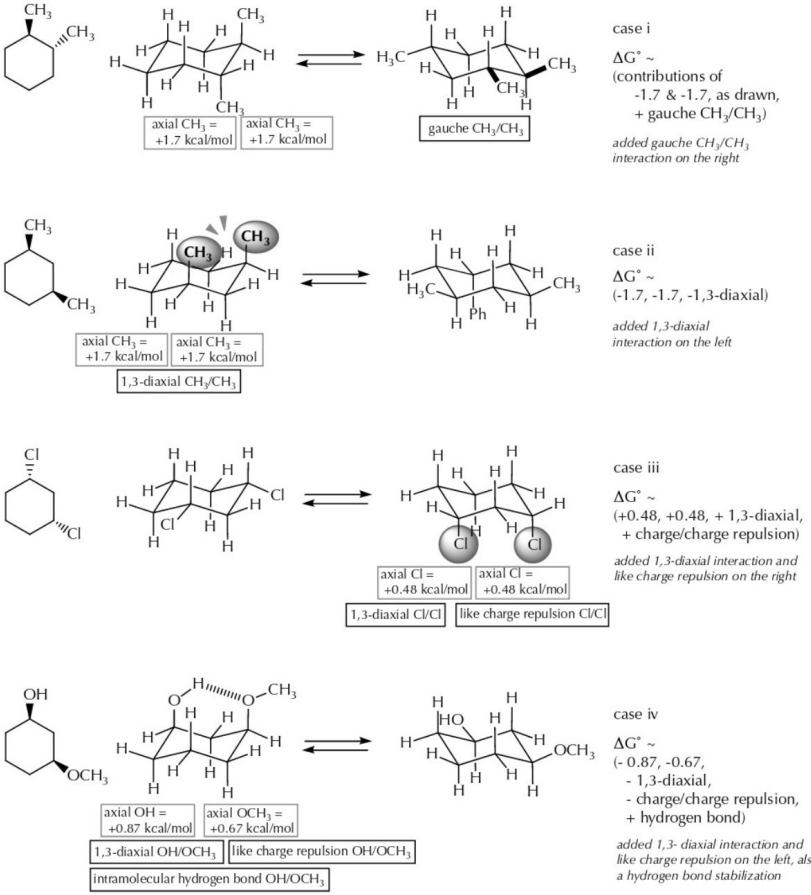
However, as illustrated in Figure 0637, two adjacent equatorial groups can experience an additional gauche interaction between them (case i), two axial groups on the same face of a molecule can experience additional steric hindrance called a 1,3-diaxial interaction (case ii), two electronegative atom groups can experience 1,3-diaxial repulsion plus an additional charge/charge repulsion (case iii), and in case iv, the two axial groups have 1,3-diaxial repulsion plus a charge/charge repulsion, but this is counteracted by an intramolecular hydrogen bond that can help stabilize the diaxial conformation (because they can reach each other when they are both axial and on the same side, but not when they are equatorial). In all of these cases, additional experimental information would be required to estimate the energy difference between the two chair conformations.

Figure 0637

Some disubstituted cyclohexanes where A-Values alone cannot be used reliably.


axial CH3 = +1.7 kcal/mol
axial CH3 = +1.7 kcal/mol
gauche CH3/CH3
case i
ΔG° ~ (contributions of -1.7 & -1.7, as drawn, + gauche CH3/CH3)
added gauche CH3/CH3 interaction on the right
axial CH3 = +1.7 kcal/mol
axial CH3 = +1.7 kcal/mol
1,3-diaxial CH3/CH3
case ii
ΔG° ~ (-1.7, -1.7, -1,3-diaxial)
added 1,3-diaxial interaction on the left
axial Cl = +0.48 kcal/mol
axial Cl = +0.48 kcal/mol
1,3-diaxial Cl/Cl
like charge repulsion Cl/Cl
case iii
ΔG° ~ (+0.48, +0.48, + 1,3-diaxial, + charge/charge repulsion)
added 1,3-diaxial interaction and like charge repulsion on the right
axial OH = +0.87 kcal/mol
axial OCH3 = +0.67 kcal/mol
1,3-diaxial OH/OCH3
like charge repulsion OH/OCH3
intramolecular hydrogen bond OH/OCH3
case iv
ΔG° ~ (- 0.87, -0.67, - 1,3-diaxial, - charge/charge repulsion, + hydrogen bond)
added 1,3- diaxial interaction and like charge repulsion on the left, also a hydrogen bond stabilization

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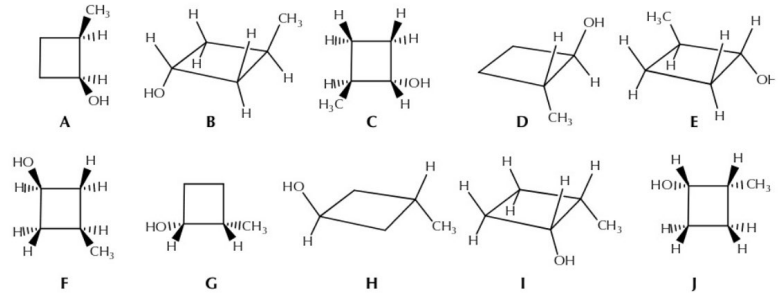
PRACTICE QUESTIONS

6.10 In the following four sets of drawings, only planar representations are used. Within each set, find the subsets of molecules that are identical (a subset may have only one member).

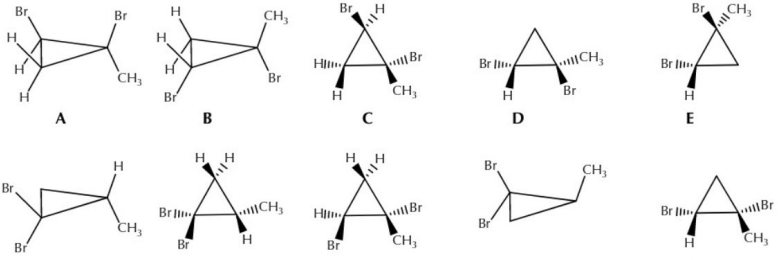
(a)



Enter an "X" into the grid corresponding to the letters of the molecular structures that are identical. Because "A" is identical to "A" and "B" is identical to "B," etc., those are already marked.

	A	B	C	D	E	F	G	H	I	J
A	X									
B		X								
C			X							
D				X						
E					X					
F						X				
G							X			
H								X		
I									X	
J										X

(b)



Enter an "X" into the grid corresponding to the letters of the molecular structures that are identical. Because "A" is identical to "A" and "B" is identical to "B," etc., those are already marked.

	A	B	C	D	E	F	G	H	I	J
A	X									
B		X								
C			X							
D				X						
E					X					
F						X				
G							X			
H								X		
I									X	
J										X

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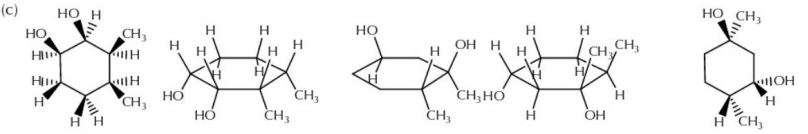
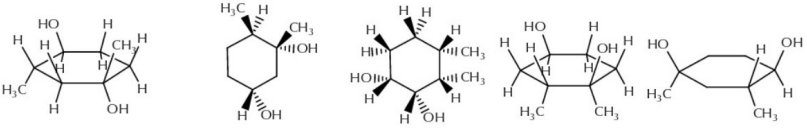
6.10 (cont.) In the following four sets of drawings, only planar representations are used. Within each set, find the subsets of molecules that are identical (a subset may have only one member).

(c)



A B C D E

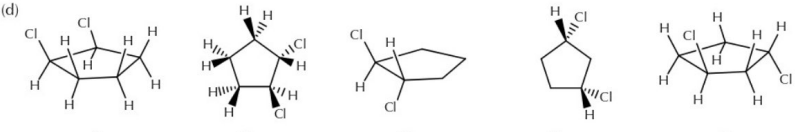


F G H I J

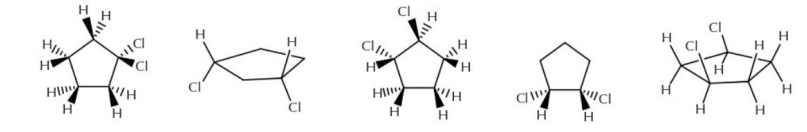
Enter an "X" into the grid corresponding to the letters of the molecular structures that are identical. Because "A" is identical to "A" and "B" is identical to "B," etc., those are already marked.

	A	B	C	D	E	F	G	H	I	J
A	X									
B	—	X								
C	—	—	X							
D	—	—	—	X						
E	—	—	—	—	X					
F	—	—	—	—	—	X				
G	—	—	—	—	—	—	X			
H	—	—	—	—	—	—	—	X		
I	—	—	—	—	—	—	—	—	X	
J	—	—	—	—	—	—	—	—	—	X

(d)



A B C D E



F G H I J

Enter an "X" into the grid corresponding to the letters of the molecular structures that are identical. Because "A" is identical to "A" and "B" is identical to "B," etc., those are already marked.

	A	B	C	D	E	F	G	H	I	J
A	X									
B	—	X								
C	—	—	X							
D	—	—	—	X						
E	—	—	—	—	X					
F	—	—	—	—	—	X				
G	—	—	—	—	—	—	X			
H	—	—	—	—	—	—	—	X		
I	—	—	—	—	—	—	—	—	X	
J	—	—	—	—	—	—	—	—	—	X

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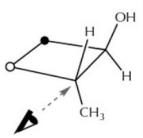
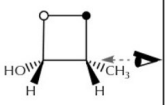
6.11 Draw the Newman projection for the following planar conformations according to the point of view indicated by the "eye." Some of the ring atoms are labeled with open or filled circles.

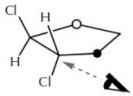
(a)



(b)

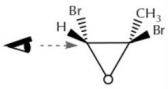


(c)

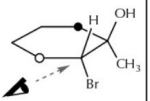


(d)

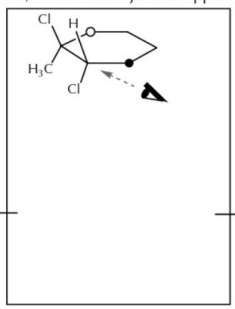
(e)



(f)



6.12 All of the ring bonds in cyclohexanes are staggered. Starting with the planar conformation, draw the Newman projection for the bond indicated with the "eye," using the implied point of view. Then, show the two Newman projections that result from partially rotating this bond from its eclipsed form into a pair of different staggered forms (in one case, the front atom moves clockwise and the back atom counterclockwise, and in the other case, the motion is just the opposite).



Partial bond rotation to give a staggered form:

Partial bond rotation to give a staggered form:

Inventory of gauche interactions for this bond:

Inventory of gauche interactions for this bond:

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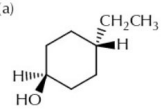
6.13 Draw the two chair conformations for the following molecules. In all of these cases, the A-Values can be used to estimate the energy difference, so also include the estimated ΔG° value for the conformational change, as you have shown it, in each case.

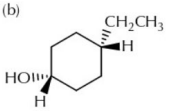
(a)



Estimated ΔG° (as shown):

kcal/mol

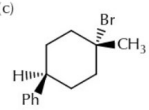
(b)



Estimated ΔG° (as shown):

kcal/mol

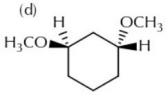
(c)



Estimated ΔG° (as shown):

kcal/mol

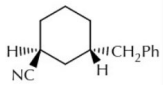
(d)



Estimated ΔG° (as shown):

kcal/mol

(e)



Estimated ΔG° (as shown):

kcal/mol

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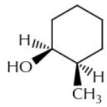
6.14 In the following cases, the A-Values alone do not provide an accurate estimate for the ΔG° because of additional interactions that can take place. (i) Draw the two chair conformations for each molecule. (ii) Identify what and where the additional interactions are in each form. (iii) Tell what the effect of the additional interaction(s) will be on any conformation where they exist.

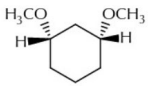
(a)



Identify what and where the additional interactions are in each form.

Tell what the effect of any additional interaction(s) will be.

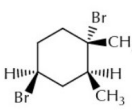
(b)



Identify what and where the additional interactions are in each form.

Tell what the effect of any additional interaction(s) will be.

(c)



Identify what and where the additional interactions are in each form.

Tell what the effect of any additional interaction(s) will be.

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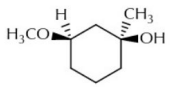
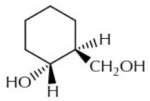
6.14 (cont.) In the following cases, the A-Values alone do not provide an accurate estimate for the ΔG° because of additional interactions that can take place. (i) Draw the two chair conformations for each molecule. (ii) Identify what and where the additional interactions are in each form. (iii) Tell what the effect of the additional interaction(s) will be on any conformation where they exist.

(d)



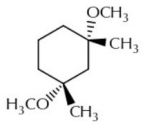
		⇌
Identify what and where the additional interactions are in each form.		
Tell what the effect of any additional interaction(s) will be.		

(e)



		⇌
Identify what and where the additional interactions are in each form.		
Tell what the effect of any additional interaction(s) will be.		

(f)



		⇌
Identify what and where the additional interactions are in each form.		
Tell what the effect of any additional interaction(s) will be.		

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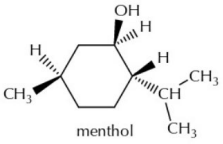
6.15 Menthol is a naturally occurring compound found in the oils of the mint tree *Mentha arvensis*. Menthol is well known for its cooling effects and its mint flavor and odor, which are the basis of the majority of its uses. The single largest use for menthol is probably in cigarettes. A survey of pharmaceutical products indicates that menthol is formulated in over-the-counter rubs and liniments (2–10% concentrations), antipruritic lotions, nasal sprays, expectorants, mouthwashes and sprays, cough drops, and foot powders.



menthol

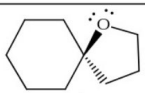
(a) Draw the two chair conformations of menthol.

less stable chair form | *more stable chair form*

(b) The experimentally determined conformational energy difference between the two chair forms of menthol is quite consistent with the value estimated from the A-Values of the three substitutent groups. What is the estimated ΔG° for the equilibrium, as shown above?

(c) Both of the chair conformations have additional interactions beyond those accounted for by the A-Values. What are these interactions, and what is the conclusion about the relative magnitude of these interactions, based on the fact that the energy difference based on the A-Values alone does a good job reproducing the experimental result for the energy difference?

6.16 Draw the two chair conformations for the molecule shown to the right. Simply think about the 5-membered ring as though it was two substitutent groups on the cyclohexane ring that happen to be connected together. Select some appropriate A-Values to estimate the ΔG° for this equilibrium.



Estimate for ΔG° based on A-Values:

kcal/mol

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6.3 Stereoisomerism and Fluxional Behavior

A. Acyclic Compounds

Up to this point, we have only considered the stereochemical analysis of separate and distinct molecules that exist in the rigid, fixed geometries we call configurations, such as in (*R*)- and (*S*)- or (*E*)- and (*Z*)-stereoisomers. Under normal conditions, these geometries will, as stated earlier in the chapter, be here tomorrow if you put the molecules in a flask today.

In this chapter, you have been introduced to molecular conformations, shapes that are flexible and changing dynamically through full and partial bond rotations. Fluxional is the word used for the opposite of rigidly fixed arrangements in molecules. Fluxional behavior is the concept that a molecule is changing its shape dynamically at the conditions under which it is being observed. Bond rotations are an example of fluxional behavior.

The transformation of one staggered form of a bond to another staggered form in ethane, for example, proceeds through an eclipsed transition state with its accompanying activation energy. The magnitude of the activation energy relative to the available energy dictates whether the bond rotation is happening rapidly, slowly, or not at all. If a bond is freely rotating under typical laboratory conditions, then the resulting 3D arrangements are its conformations. Temperature, in particular, plays an important role in the process of bond rotations. In practice, you can lower the temperature of a sample enough so that there is not enough energy available for the bond rotation to happen (or perhaps to happen slowly) and study it in its more rigidly fixed form.

Although they are interconverting rapidly and have short lifetimes, the individual conformations that exist during a bond rotation are also molecular geometries. As geometries, the individual conformations can be the subject of stereochemical analysis, and the relationship between two conformations can be classified exactly the same way as in the case of stereoisomeric configurations, namely, as "identical conformations," "enantiomeric conformations," or "diastereomeric conformations."

Revisiting the conformations of butane. Starting with the conformation of the C_2-C_3 bond of butane where the two methyl groups are anti, a 120° turn to left creates one of the conformations where the methyl groups are gauche, while a 120° turn to the right creates another gauche form. Energetically, the two gauche conformations of butane are identical, but geometrically they are not. One of them was formed with a right-handed twist and the other was formed with a left-handed twist. As is true with any spiral, the right- and left-handed twist creates a chiral object. In this case, the two gauche conformations are not stereochemically identical, but rather they are enantiomeric (Figure 0638 on the next page). You should construct a pair of molecular models of these two gauche forms to truly convince yourself that they are nonidentical geometries, and to see the enantiomeric relationship. There is a diastereomeric relationship between either of the gauche conformations and the more stable anti conformation. The anti conformation is achiral (its mirror image is identical to itself).

We are imaging the isolated and frozen-in-place conformations and defining their stereochemical properties (chirality) and the stereochemical relationships between them (identical, enantiomeric, diastereomeric). The two gauche butane conformations are chiral because they represent nonidentical, mirror image, right- and left-handed twists. And at the same time, a sample of butane is also certainly optically inactive, and we correctly identify it as an achiral molecule. This is not a contradiction, but instead a common reality in molecules. During bond rotations, molecules are constantly interconverting between enantiomeric shapes.

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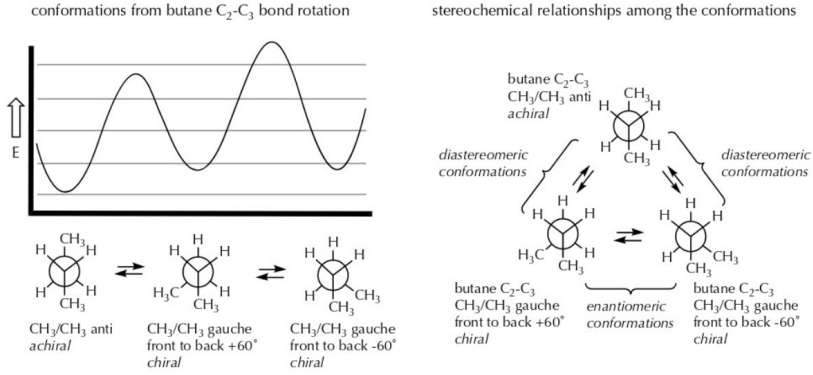
Figure 0638

Stereochemical relationships among the three C_2-C_3 butane conformations.

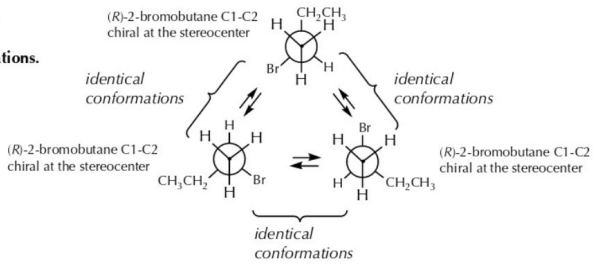


Recall that the highest energy rotational barrier in butane, the conformation with two eclipsed methyl groups, is 4.5 kcal/mol above the lowest energy staggered form. Recall too that, at room temperature, processes with activation energies less than 25–30 are happening rapidly. Under those normal experimental conditions, butane is undergoing about 10^9 bond rotations per second. The three butane conformations are in such rapid equilibrium that, during any measurement we make, the two enantiomeric gauche forms are not only in a 1:1 mixture, because they are energetically identical, but also the one with the right-handed twist literally becomes the one with the left-handed twist in less that 10^{-9} seconds! As we make an observation of butane, in other words, the C_2-C_3 is freely and rapidly rotating, interconverting at an incredible rate between its anti conformation and its two enantiomeric gauche conformations.

Keep the distinction between configurations and conformation. The stereochemical analysis for the stereoisomers of a given connectivity is separate and distinct from the stereochemical analysis of an individual molecule's conformations (as long as the stereoisomers are not also interconverting under the experimental conditions). Butane is an achiral molecule whose C_2-C_3 bond is described as three rapidly interconverting conformations: two gauche forms that are chiral and have an enantiomeric relationship, and the single anti form that is achiral and has a distereomeric relationship with either of the gauche conformations.

Figure 0639

Stereochemical relationships among the three C_1-C_2 (*R*)-2-bromobutane conformations.



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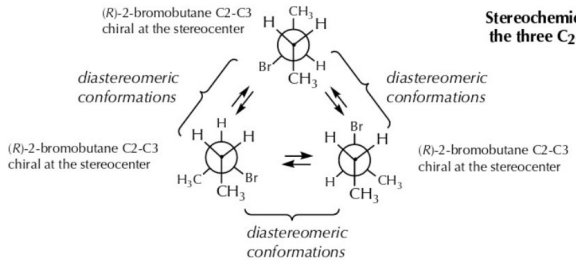
(*R*)-2-Bromobutane is a chiral molecule that has an enantiomer, (*S*)-2-bromobutane. A conformational analysis does not change that configurational fact, and each bond can be analyzed independently of the others. (*R*)-2-Bromobutane has three staggered conformations for its C_1-C_2 bond that are identical (Figure 0639) because of the three hydrogen atoms on carbon-1. The ratio of these three conformations would be expected to be 1:1:1.

On the other hand, while the C_2-C_3 bond of (*R*)-2-bromobutane (Figure 0640) also has three staggered conformations, they are all mutually diastereomeric thanks to the relationship between the groups attached to the stereocenter (carbon-2) and the carbon-4 methyl group. The three conformations for the C_2-C_3 bond are nonequivalent and can be evaluated for their relative populations (the methyl/bromo gauche interaction has less steric hindrance than the methyl/methyl interaction, and both of these are lower in energy than the conformation with the two gauche interactions.

Figure 0640

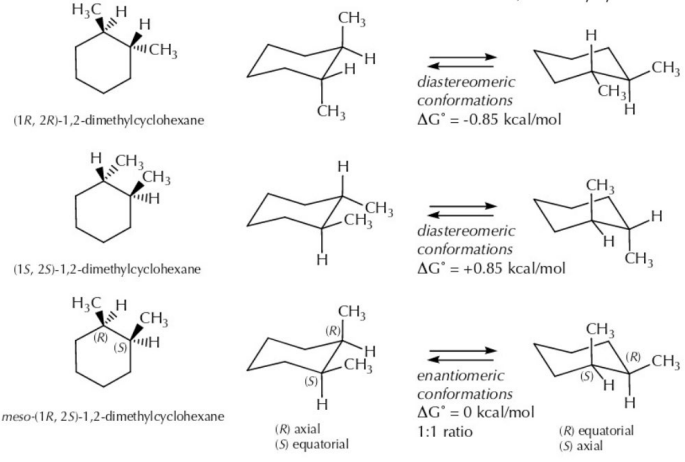

(R)-2-bromobutane C2-C3 chiral at the stereocenter
diastereomeric conformations
diastereomeric conformations
(R)-2-bromobutane C2-C3 chiral at the stereocenter
(R)-2-bromobutane C2-C3 chiral at the stereocenter
diastereomeric conformations

Stereochemical relationships among the three C_2-C_3 (*R*)-2-bromobutane conformations.

B. Cyclic Compounds

There are three stereoisomers of 1,2-dimethylcyclohexane, and the pair of chair conformations for each one is shown in Figure 0641.

Figure 0641



Stereochemical relationships among the chair conformations of the three 1,2-dimethylcyclohexane stereoisomers.

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The two chiral compounds, (1*R*, 2*R*)-1,2-dimethylcyclohexane and its enantiomer, (1*S*, 2*S*)-1,2-dimethylcyclohexane, are accompanied by the achiral *meso* compound, (1*R*, 2*S*)-1,2-dimethylcyclohexane. The conformational analysis for all three stereoisomers involves the comparison of the relative stability of and relationship between each of their two chair forms.

The three pairs of chair conformations for the three stereoisomers are shown in Figure 0641. The two chair conformations for the (1*R*, 2*R*)-1,2-dimethylcyclohexane are chiral and diastereomeric, where the form with the two equatorial methyl groups is more stable than the form with the two axial methyl groups. The situation for the conformations of its enantiomer, the (1*S*, 2*S*)-1,2-dimethylcyclohexane stereoisomer, is comparable. Its two conformations are chiral and diastereomeric.

Note that the two more stable conformations for (1*R*, 2*R*)- and (1*S*, 2*S*)-1,2-dimethylcyclohexane are both forms with two equatorial methyl groups. The only relationship between these two specific conformations is that they are different molecules, derived from the (1*R*, 2*R*)- and (1*S*, 2*S*)-enantiomers of 1,2-dimethylcyclohexane, and they happen to have the same relative energies because they are enantiomers. They are not enantiomeric or identical conformations because they are not conformations of the same molecule; they are enantiomers because they are different molecules, regardless of their conformations.

The pair of chair conformations for the *meso* stereoisosmer, (1*R*, 2*S*)-1,2-dimethylcyclohexane, are enantiomeric. As in the case of the two gauche butane conformations, the individual conformations are chiral, but the molecule itself is achiral because the molecule is rapidly interconverting between these two enantiomeric conformations, in a 1:1 ratio, under normal experimental conditions.

The bottom line: The *meso* compound is achiral, as previously claimed, and its two enantiomeric chair conformations are rapidly interconverting and maintaining a 1:1 ratio.

C. Nitrogen, Sulfur, and Phosphorus Stereocenters

Bond rotations are not the only fluxional behavior in molecules. Any tetrahedral atom with four different groups around it can be a stereocenter, even for molecules where one of those groups is a nonbonding electron pair.

An uncharged sp^3 nitrogen atom with three different substituent groups ought to possess (*R*)- and (*S*)- geometries, and they do (a nonbonding electron pair has the lowest priority for creating the geometrical label, as it is treated as a bond with an atom whose mass is zero). Observations of optically active nitrogen compounds of this type are quite rare, however, because the nonbonding electron pair allows for a process that it not possible at a tetravalent carbon atom: The nitrogen can undergo a rapid equilibrium between its enantiomeric forms through a low energy rehybridization via an sp^2 intermediate (Figure 0642). This is called a nitrogen inversion, and the activation energy for simple nitrogen compounds is about 7–8 kcal/mol. The nitrogen atom is rapidly interconverting between its two enantiomeric forms, and the compound is not observed to be optically active. The nitrogen inversion process is not limited to atoms that are possible stereocenters. Even ammonia (NH_3) has been studied, and it is estimated to invert about 3 billion times a second, at room temperature, with an activation energy of 5 kcal/mol.

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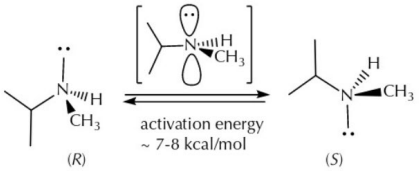
Figure 0642

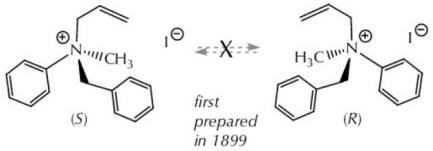
Rapid rehybridization equilibrium at sp^3 nitrogen atoms.



Quaternary ammonium salts do not have this inversion mechanism available to them, and the enantiomers can be separated, isolated, and stored as configurationally stable compounds (Figure 0643).

Figure 0643

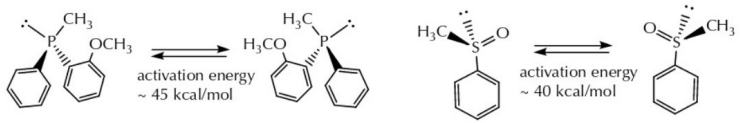
Configurationally stable quaternary ammonium compounds.



Other heteroatoms share these same properties. Whether or not the enantiomeric forms are observable under normal experimental conditions depends on the activation energy for the interconversion, called the inversion barrier, between the forms. The barrier for third row elements (S and P) is higher than for nitrogen atoms, and many configurationally stable examples of chiral compounds involving those atoms are known (Figure 0644). When the activation energies for the barrier to inversion are greater than about 25 kcal/mol, the stereoisomers derived from the heteroatom stereocenter can generally be observed.

Figure 0644

Representative examples of heteroatom stereocenters and their fluxional properties.



D. Alkenes, Amides, and Esters

Most double bonds are configurationally stable. In typical alkenes, the barrier to rotation around the double bond is high (about 40–65 kcal/mol) because the pi bond needs to break before the bond can turn. In Figure 0601, the low energy barrier for breaking the pi bond in (*E*)-cycloheptene, resulting in (*Z*)-cycloheptene, is described. There are some pi bonds that are weak, and for which fluxional behavior is observed.

A pi bond that is flanked by both an electron donating group and an electron-withdrawing group will have a highly significant resonance contributor with single bond character. The molecule shown in Figure 0645 is an example of such a "push-pull" alkene, and it is configurationally unstable under normal experimental conditions. The activation energy for the bond rotation, which interconverts the diastereomeric (*E*) and (*Z*) forms, is 16–19 kcal/mol.

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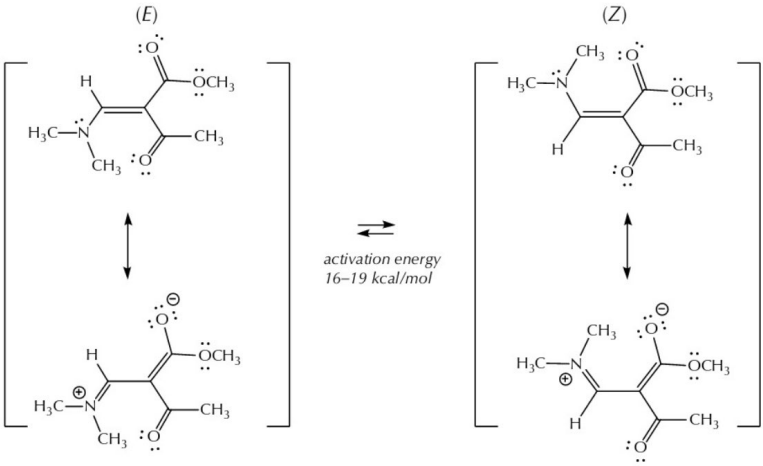
Figure 0645

Fluxional behavior in a "push-pull" pi bond.

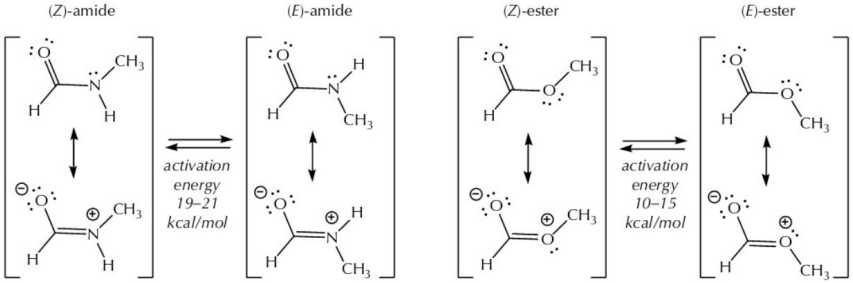


Although we draw amides and esters with a single bond between the carbon in the C=O and the nitrogen and oxygen atoms, respectively, the molecules are experimentally observed to have two different geometrical forms that are interconverting under normal conditions (Figure 0646). The contribution for the resonance contributor with the carbon-nitrogen pi bond, in the case of the amide, is more relatively significant than in the case of the comparable carbon-oxygen bond in the ester. The less electronegative nitrogen atom can better handle a positive charge in the amide than the corresponding oxygen atom can in the ester.

When the two interconverting forms are not identical, they are diastereomeric, and the (*E*)- and (*Z*)- labels are used to describe their geometries, where one of them is often significantly more stable than the other. Collectively, the different but relatively stable molecular structures resulting from these bond rotations are called rotamers (rotational isomers).

Figure 0646

Fluxional behavior in amides and esters.



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We return now to where we began: This introduction to fluxional behavior, starting with bond rotations and including some of these more sophisticated topics on atom inversions, all form the foundation for studying the complex Grand Challenge of the folding problem in large biomolecules.

You have now seen cases where up to four factors are needed to account for the conformation preference of a single carbon-carbon bond, and that these factors have no intrinsic ranking in their contributions. In the cyclohexane chair form, we effectively look at six bonds simultaneously, and we can only do that at the introductory level because the system is so well-behaved, with a single, common, low-energy conformation.

In this introduction, we never even attempted to analyze a molecule's overall conformation by trying to combine two Newman projects and to consider the effect of how a bond rotation in one part of a molecule affects the rotation in another bond.

So now imagine the situation in a relatively small protein: 150 amino acids, each amino acid with 10–15 bonds that can rotate, with a total of 1,500–2,500 bonds to study. Ionic effects might be hundreds of charges and partial charges spread apart over long distances. A hydrogen bond donor might be 75 atoms away from its acceptor site. And the thousands of nearby water molecules are interacting differently with the hydrophilic and hydrophobic segments of the protein, which also needs to be taken into account.

You would now recognize most if not all of the factors that the computer programs working on these problems take into account. And it is not surprising that artificial intelligence networks are needed to advance the work, as even knowing how to take those factors into account needs to be built upon huge data sets of experimental results.

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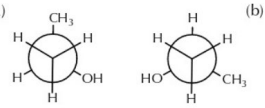
PRACTICE QUESTIONS

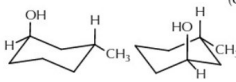
6.17 The following pairs of drawings are either conformations of the same molecule, in which case they have an identical, enantiomeric, or diastereomeric relationship, or they are different molecules altogether, in which case the drawings have no conformational relationship. Identify whether these are the same or different molecules, and if they are the same molecule, then what is the stereochemical relationship between the conformations?

(a)



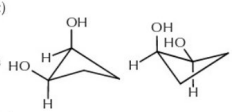
- ☐ identical conformations
- ☐ enantiomeric conformations
- ☐ diastereomeric conformations
- ☐ different molecules

(b)



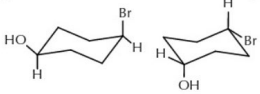
- ☐ identical conformations
- ☐ enantiomeric conformations
- ☐ diastereomeric conformations
- ☐ different molecules

(c)



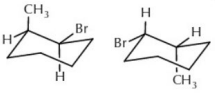
- ☐ identical conformations
- ☐ enantiomeric conformations
- ☐ diastereomeric conformations
- ☐ different molecules

(d)



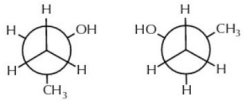
- ☐ identical conformations
- ☐ enantiomeric conformations
- ☐ diastereomeric conformations
- ☐ different molecules

(e)



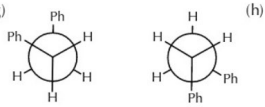
- ☐ identical conformations
- ☐ enantiomeric conformations
- ☐ diastereomeric conformations
- ☐ different molecules

(f)



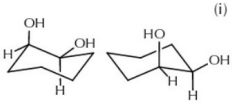
- ☐ identical conformations
- ☐ enantiomeric conformations
- ☐ diastereomeric conformations
- ☐ different molecules

(g)



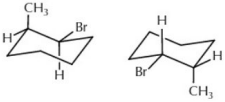
- ☐ identical conformations
- ☐ enantiomeric conformations
- ☐ diastereomeric conformations
- ☐ different molecules

(h)



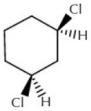
- ☐ identical conformations
- ☐ enantiomeric conformations
- ☐ diastereomeric conformations
- ☐ different molecules

(i)



- ☐ identical conformations
- ☐ enantiomeric conformations
- ☐ diastereomeric conformations
- ☐ different molecules

6.18 A *meso* stereoisomer is achiral. The two chair conformations for *meso*-(1*R*, 2*S*)-1,2-dichlorocyclohexane are enantiotopic, while the two chair conformations for *meso*-(1*R*, 3*S*)-1,3-dichlorocyclohexane are diastereotopic. Draw these conformations and explain how these differences in the relationships between the chair conformations are not at all inconsistent with the molecules being classified as achiral.



explanation:

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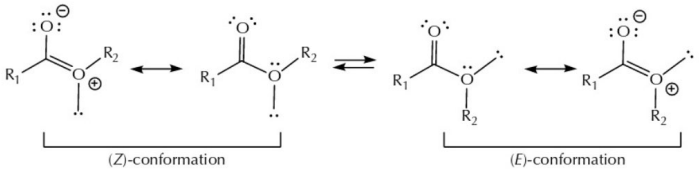
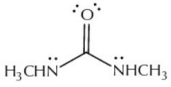
6.19 The partial double bond character in esters results in two low-energy conformations that are both planar, and where the conformational labels (*Z*)- and (*E*)- are used. The activation energy for these forms to interconvert is low (10–15 kcal/mol) and so the equilibrium is easily observed under normal experimental conditions.



In methyl formate (R_1=H, R_2=CH_3), the (*E*)-conformation is 4.3 kcal/mol more stable than the (*Z*)-conformation, but in methyl acetate (R_1=CH_3, R_2=CH_3), the (*E*)-conformation is about 8 kcal/mol less stable than the (*Z*)-conformation.

(a) Explain this observation.

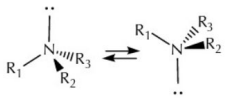
(b) Based on the results above, predict the geometry of the three low energy, planar conformations for 1,3-dimethylurea and rank them from most stable to least stable.



1,3-dimethylurea

most stable conformation		*least stable conformation*

6.20 The nitrogen inversion barrier for interconverting a sp^3 nitrogen atom into its companion has relatively low activation energy (typically 7–8 kcal/mol). The inversion barrier for isopropylamine [$(CH_3)_2CHNH_2$, classified as a primary amine] is right in this range. By contrast, the inversion barrier for tertiary amines such as ethyl diisopropylamine [$((CH_3)_2CH)_2NCH_2CH_3$] is even lower, oftentimes just 0–1 kcal/mol. Explain this observation.



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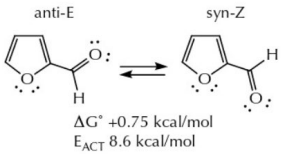
6.21

A. The following molecule is observed to have two low-energy, planar conformations called syn-Z and anti-E. The anti-E form is 0.75 kcal/mol more stable than the syn-Z form, and the inverconversion barrier is 8.6 kcal/mol. Explain, using structural drawings, why these two planar conformations are observed, why the anti-E form is more stable, and whether you would expect to see fast or slow interconversion at room temperature.

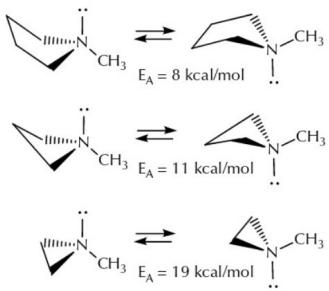


Why are these two planar conformations observed?

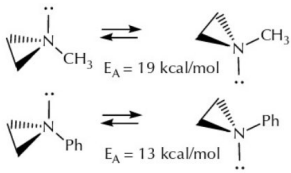
Why is the anti-E form more stable?

Fast or slow interconversion at room temperature? Why?

B. In nitrogen heterocycles, the nitrogen inversion barrier increases as the size of the ring containing the nitrogen atom decreases. Explain the trend in the activation energies for this process in the series of compounds below.



C. In nitrogen heterocycles, the nitrogen inversion barrier is affected by the identity of the group on the nitrogen atom. Explain the difference in the activation energies for this process in the pair of compounds, below.



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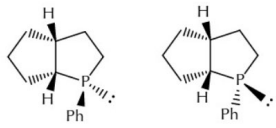
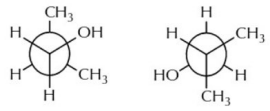
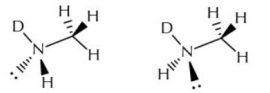
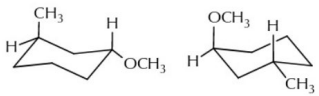
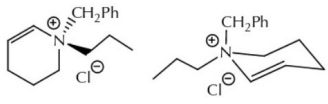
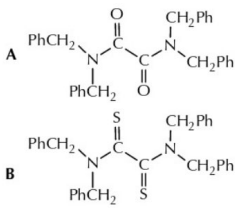
6.22

A. Under normal experimental conditions, do the following drawings represent a single molecular substance because they are forms that are interconverting, or do they represent different substances that could be separated and isolated, and which are slow to interconvert (under normal conditions)? If they are a single molecule, do the drawings represent identical, enantiomeric, or diastereomeric forms? If they are different, are they enantiomers or diastereomers?

	single substance (interconverting forms)	different substances (not interconverting)
(a) 	☐ identical ☐ enantiomeric ☐ diastereomeric	☐ enantiomers ☐ diastereomers
(b) 	☐ identical ☐ enantiomeric ☐ diastereomeric	☐ enantiomers ☐ diastereomers
(c) 	☐ identical ☐ enantiomeric ☐ diastereomeric	☐ enantiomers ☐ diastereomers
(d)	☐ identical ☐ enantiomeric ☐ diastereomeric	☐ enantiomers ☐ diastereomers
(e) 	☐ identical ☐ enantiomeric ☐ diastereomeric	☐ enantiomers ☐ diastereomers
(f) 	☐ identical ☐ enantiomeric ☐ diastereomeric	☐ enantiomers ☐ diastereomers

B. The N-C-C-N dihedral angle is 180° in the most stable conformation of compound A, with an activation energy for the C-C bond rotation of 9.7 kcal/mol. In compound B, the N-C-C-N angle is 90°, and the activation energy for the C-C bond rotation is over 24 kcal/mol. What is a reasonable explanation for this difference?



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Reflections About Science: Axial and Equatorial

The two most abundant organic compounds in the world are cellulose and starch. They are both derived from glucose, and they differ, structurally, because of an axial versus equatorial bond.

Glucose is a carbohydrate. Carbohydrates are one of the main macronutrients needed in a normal diet. The name "carbohydrate" comes from the early experimental analysis of the elemental composition, which gave a 1:1 ratio between carbon and water, hence $C_n(H_2O)_n$ or a form of hydrated carbon. Before its structure was known, naturally occurring glucose was observed to be optically active and its molecular stereochemistry was experimentally related to a chiral dextrorotatory molecule that was used as a reference point, and so natural glucose was also called D-glucose (indicating its relationship to the dextrorotatory reference). Coincidentally, natural glucose is also dextrorotatory, and one of its historical synonyms is dextrose. Naturally occurring glucose also occurs in two forms, called alpha (α) and beta (β), depending on whether a specific hydroxyl group is trans (α) or cis (β) to the CH_2OH group on the ring. Thus, the six-membered ring forms of (axial OH) α-D-glucose and (equatorial OH) β-D-glucose diastereomers are shown in Figure 0647.

Figure 0647

Naturally occurring α-D-glucose and β-D-glucose.

naturally occuring α-D-glucose

naturally occuring β-D-glucose

Cellulose is the most abundant organic molecule in the world. Cellulose is a polymer in which hundreds to thousands of β-D-glucose molecules are bonded together into linear chains. Plants make glucose, then cellulose, through the process of photosynthesis, using carbon dioxide as a source of carbon, combining it with water, and ejecting a molecule of oxygen as a byproduct. Cellulose is the major component in the cell walls of plants and makes up about 33% of all vegetable matter. The cellulose content of cotton is about 90%, while that of wood is about 45%.

Starch is the second most abundant organic molecule in the world. Starch is also a polymer in which hundreds of α-D-glucose molecules are bonded together. Starch is also produced by most green plants and stored in their cells as small grains or granules. Starch is abundant in potatoes, wheat, rice and other staple foods. The chains can be linear (amylose) or branched (amylopectin) and contain as few as a hundred glucose molecules or many tens of thousands, depending on the source. The structural comparison between cellulose and starch (amylose) is shown in Figure 0648.

In the human body, a chemical reaction between starch and water takes place, in which the individual glucose molecules are released from the polymeric structure (called a hydrolysis reaction—to break apart with water). Specific molecular catalysts, proteins called enzymes, are required for these reactions to take place (Figure 0649). The hydrolysis process begins in your mouth, where enzymes called salivary amylases begin the digestive process. Chewing breads, potatoes, or rice overly long can produce a slightly sweet taste in your mouth as one of the common, initial hydrolysis products is maltose, which is classified as a disaccharide, and is an example of a sugar (literally named malt sugar, from its discovery in malt barley).

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Figure 0648
Cellulose and starch.

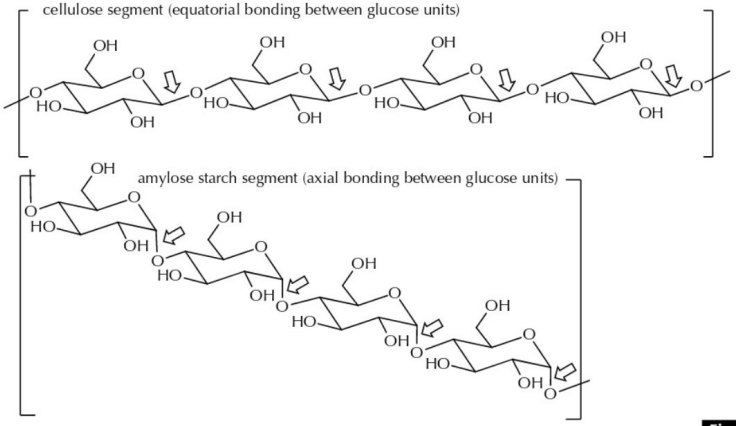
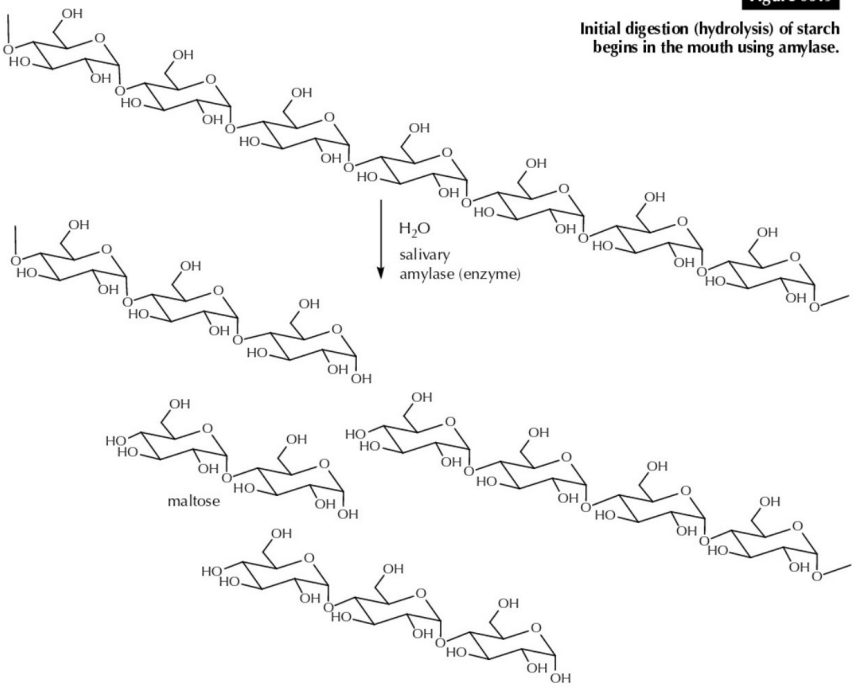

cellulose segment (equatorial bonding between glucose units)
amylose starch segment (axial bonding between glucose units)

Figure 0649
Initial digestion (hydrolysis) of starch begins in the mouth using amylase.



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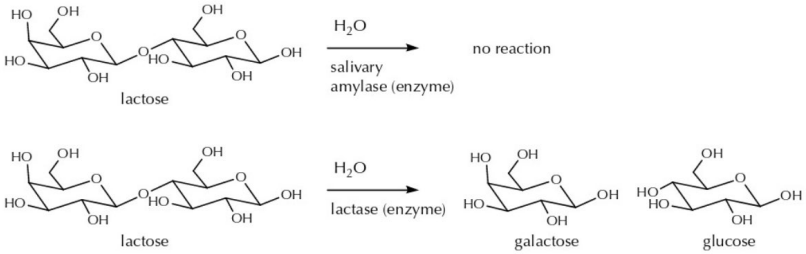
Paper, cotton, and other cellulose-based plant products, collectively called fiber, are not digestible. The enzymes that catalyze the hydrolysis reaction with the axial bonds in starch cannot function on the equatorial bonds in cellulose. This high degree of selectivity is common in biochemistry. Enzymes are molecules that generally need to wrap in quite specific ways, and maintain close contact, to function correctly. Enzymes that can act upon the nonlinear molecular shape of starch, with its axial bonds, cannot interact productively with the linear cellulose structure. Cellulose (insoluble fiber) molecules, because of these equatorial bonds, simply pass through a body's digestive tract and are unavailable for nutrient value.

Another interesting case of axial versus equatorial bonding is lactose. Like maltose (above), lactose is a disaccharide and also called a sugar; in this case, the name lactose means milk sugar. As you can see in its molecular structure (Figure 0650), lactose is made up of two six-membered rings. As drawn, the one on the right is derived from glucose and the one on the left, with one of its ring hydroxyl groups in the axial position, is derived from another sugar named galactose.

The right-hand (glucose) ring is bonded to the galactose ring through an equatorial bond, such as the ones in cellulose. Consequently, the usual enzymes that catalyze the hydrolysis of the equatorial bonds in starch cannot catalyze the equatorial bond in lactose. Instead, a quite specific enzyme, called lactase, is required to be able to digest (hydrolyze) lactose into its component glucose and galactose molecules. Lactase is so specific for the lactose molecule that it cannot interact productively with anything else, including cellulose.

Figure 0650

Digestion (hydrolysis) of lactose requires lactase.



You or someone you know may be "lactose intolerant." This means that your body is not producing sufficient amounts of the lactase enzyme to hydrolyze lactose molecules. Just as in the case of cellulose, the equatorial bonding renders the lactose molecule indigestible by the normal hydrolysis reaction process. Anaerobic bacteria in the digestive tract can use lactose for fermentation, however, and eating even modest amounts of dairy products can result in severe gastrointestinal distress for people without enough lactase in their bodies. Some milk products come with added lactase, and it is also possible to take lactase in pill form prior to eating dairy products, in both cases so that the lactose can be digested.

The majority of people in the world have some degree of lactose intolerance because this is the original natural state for mammals. For eons, the only readily available milk was available to infants from their mothers. After weaning, the need for lactase effectively disappeared, and its activity generally diminished dramatically or disappeared by adulthood. According to molecular biological studies, lactose tolerance appeared only 7,500–9,000 years ago, and corresponds to the rise in dairy farming with domesticated animals such as cows, sheep, and goats, which began in the Middle East and northern Africa and moved

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into Europe. A specific genetic variation (mutation) allowed some people to continue to produce lactase into adulthood. Without dairy products available, having this mutation provided no particular advantage. On the other hand, introducing milk, and then cheese, into the diet is thought to have nutritionally advantaged those with the lactose tolerance mutation, and their improved mortality enabled them to pass this trait on to their children with disproportionate reproductive success. The lactose tolerance mutation is not at all common in parts of the world, such as East Asia, where dairy farming did not emerge in their agricultural history.

Summary

The carbon chains in noncyclic hydrocarbons assume different conformations through rotations around the carbon–carbon single bonds. Staggered conformations are more stable than eclipsed conformations because, in the latter, bonds on adjacent carbon atoms are aligned with each other and, therefore, repel each other.

Gauche interactions in staggered conformations can be destabilizing (steric hindrance, same charge repulsion) or stabilizing (opposite charge attraction, intramolecular hydrogen bonding), which affects the equilibrium distribution of the staggered forms. In general, experimental data are needed to resolve the conflict in evaluating the balance of stabilizing and destabilizing interactions.

The most stable conformation of cyclohexane is the chair form, which has six equatorial hydrogen atoms and six axial ones. A substituted cyclohexane is most stable when the substituent is in an equatorial position. A cyclohexane with a substituent in the axial position is destabilized by 2 gauche interactions with the ring. Additional interactions can exist when there are two or more substituent groups, including both favorable and unfavorable gauche interactions as well as 1,3-diaxial interactions. As in the case of acyclic compounds, additional information must be provided from experimental data to resolve the analysis in cases where the criteria give conflicting predictions.

Small ring compounds such as cyclopropane and cyclobutane are unstable in comparison to cyclohexane because of ring strain. Such strain is due to bond angles that are smaller than the tetrahedral angle and to the eclipsing of bonds on adjacent atoms.

Molecules exhibiting fluxional behavior include those undergoing conformational changes due to full and partial bond rotations. The stereochemical analysis of conformations leads to the identifications of relationships among conformations as enantiomeric, diastereomeric, or identical. While these analyses demonstrate that many individual conformations are chiral, even in the simplest of molecules such as butane, the rapid bond rotations interconvert one enantiomeric form to another, rendering the molecule achiral.

Weakened and partial pi bonds can rotate to allow interconversion between to two planar diastereomeric geometries called rotamers. Some electronically tetrahedral atoms with free nonbonding electron pairs can exhibit fluxional behavior, where the nonbonding electron pairs permit low-energy rehybridization equilibria that can invert heteroatom stereocenters. The inversion barrier (activation energy) depends on the structure.

Conformational analysis underlies the science behind the folding problem of large biomolecules.

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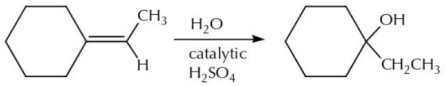
CHAPTER QUESTIONS

6.23 The electrophilic addition of water with compound G using an acid catalyst results in the product shown here (compound H) as the major regioisomer.



compound G compound H

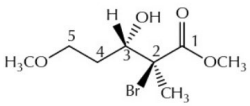
Draw the two chair conformations for compound H.
(i) be sure that your chair forms are clearly represented
(ii) include all of the hydrogen atoms on the cyclohexane ring and show their directionality clearly
(iii) the A-Value for OH is 0.87 and the A-Value for CH_2CH_3 is 1.75
(iv) what is the estimated ΔG° for this interconversion?

less stable chair form here more stable chair form here

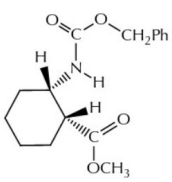
estimated ΔG°

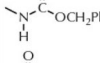
kcal/mol

6.24 Draw the Newman projection for the C_2-C_3 bond of this conformation of this molecule, using C_2 as the front atom.



6.25 The A-Values for some groups are included in a data table below. Based on these values, draw the less stable chair conformation for this molecule.



group	A-Value
	0.6
	0.5
	0.9
	1.29

estimated ΔG° for the interconversion of this chair to the more stable conformation:

kcal/mol

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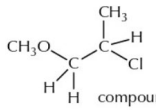
6.26 Compound P is named 1-methoxy-2-chloropropane.



compound P

(1-methoxy-2-chloropropane)

(a) Using lines, dashes, and wedges notation, draw the (*S*)-isomer of compound P:

(i) show the C1-C2 bond
(ii) show the conformation with the OCH_3 group and the Cl group anti to each other

(b) Using Newman projections, provide the three staggered conformations for the C_1-C_2 bond of the (*S*)-isomer of compound P. Place C_1 (with the methoxy group) in the front, C_2 (with the chloro group) in the back. Draw the least stable conformation in the first space. Rotate the back carbon (C_2) in a clockwise direction in order to create the other two staggered conformations. In comparison compounds, the energy of the gauche interaction for OCH_3/Cl is greater than that for OCH_3/CH_3.

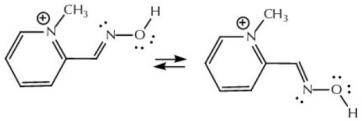
least stable conformation

(c) Does the conformation you drew in part (a) correspond the most stable, least stable, or intermediate stability staggered form for compound P?

(d) Draw the eclipsed conformation that is anticipated to form when the staggered conformation in the first answer space in part (b) interconverts with the staggered conformation in the second answer space.

(e) What is the stereochemical relationship between the staggered conformation in the first answer space in part (b) and the staggered conformation in the second answer space?

6.27 Explain the following observation:
(a) this molecule exists mainly in two planar conformations
(b) the energy required for the bond rotation (6.7 kcal/mol) is over twice the value required for ethane (3 kcal/mol)



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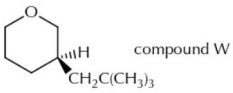
6.28 Six-membered rings can have a variety of heteroatoms in them. In general, the conformational analysis can be approached as you would for the all-carbon case.



compound W

(a) Provide a clear drawing of the LEAST stable chair conformation for compound W. Be sure to include the accurate directionality of only the groups that are shown. Also double check that you have drawn this specific stereoisomer shown above.

(b) Replacement #1:

If you replace the oxygen atom in compound W with a "CH_2" group, the energy of the least stable conformation goes up, that is, it becomes even less stable. Draw this conformation and explain why it is less stable than the one you drew in part (a).

(c) Replacement #2:

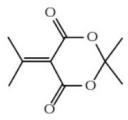
If you replace the "-$CH_2C(CH_3)_3$" group in compound W with a carboxylic acid group,

the conformation from part (a) is now the more stable one and not the less stable one. Draw this conformation and explain why it is more stable than the one you drew in part (a).

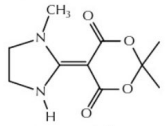
(d) Now imagine you are analyzing compound Y, which is the enantiomer of compound W. Would the least stable chair conformation of compound Y be more stable, less stable, or exactly the same in stability as the least stable chair conformation of Compound W that you drew in part (a)?

The least stable chair conformation of compound Y is:	Briefly explain:
more stable less stable exactly the same stability as the least stable chair conformation of compound W.	

6.29 The carbon-carbon double bond in compound M has a relatively normal length (1.357 Å) and normally high barrier to rotation (~45 kcal/mol). By comparison, compound N is observed to have a longer double bond (1.426 Å) and a significantly lower rotational barrier (6.6 kcal/mol). Explain this observation.



compound M



compound N

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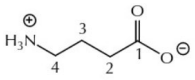
6.30 Gamma-aminobutyric acid (also commonly known as GABA) is the chief inhibitory neurotransmitter in our bodies. Its structure is shown on the right, along with the numbering scheme for its carbon atoms.

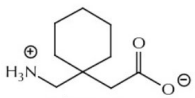


GABA

(a) Use a Newman projection to show the most stable conformation for the C_2-C_3 bond in GABA.
NOTE 1: use C_2 as the front atom
NOTE 2: it is known that the electrostatic attraction between these charged groups is greater than their steric repulsion

(b) Draw the 3D (line/dash/wedge) picture for the LEAST stable staggered conformation of the C_2-C_3 bond in GABA.

(c) Gabapentin is a molecular analogue of GABA, meaning that it was intentionally designed to have a similar overall molecular shape and function as GABA. Gabapentin is used as a drug to treat epilepsy, a disease that is related to an imbalance of GABA with other neurotransmitters in the brain. Based on the following structure, and the accompanying data table, draw the two chair conformations for gabapentin with the more stable one in the left-hand space and the less stable one in the right.



Gabapentin

Group	- NH_3	- CH_2NH_3		
A-Value	1.9	1.52	1.92	1.75

more stable chair conformation

less stable chair conformation

(d) In part (a), the second NOTE suggests that net attraction between the two oppositely charged groups is more favorable than their steric repulsion. Looking for a moment at the chair conformations in part (c), do you think it is going to be easier or harder for the positively and negatively charged groups to be closer to each other in Gabapentin compared with GABA? Explain.

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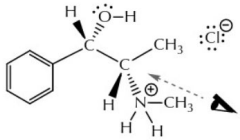
6.31 Pseudoephedrine hydrochloride is a decongestant found in many over-the-counter medicines.

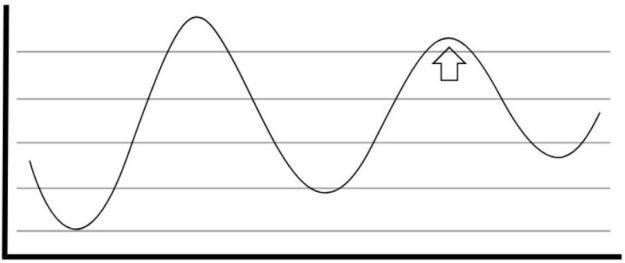
pseudoephedrine hydrochloride



(a) Draw the Newman projections for the three staggered conformations of the bond where the carbon bearing the nitrogen-atom group is the front atom and where the carbon bearing the OH group is the back atom (as indicated by the face). You may use "Ph" for the phenyl group. Conformation W is the one from above. Follow the directions in the boxes for the others.

conformation W (draw the one from above)	*conformation X* (clockwise rotation of the front carbon of conformation W by +120°)	*conformation Y* (clockwise rotation of the front carbon of conformation X by +120°)
:Cl:⊖	:Cl:⊖	:Cl:⊖

(b) Favorable intramolecular hydrogen bonding and a few unfavorable steric interactions are used to explain the relative ranking of the stability of the three conformations. Based on this information, identify which points correspond to conformations W, X, and Y on the energy diagram.



enter "W," "X," and "Y" here:

(c) Using line/dash/wedge notation, provide a drawing for the eclipsed form that sits at this second transition state, according to the conformations that you have entered into the boxes from part (b).

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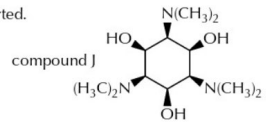
6.32 The conformations of some highly substituted cyclohexanes have been reported. The two chair conformations of compound J differ by 18 kcal/mol.



(a) Draw the two chair conformations of compound J, putting the more stable one in the right-hand space. Be sure to include all 6 substituents and the hydrogen atom groups associated with each vertex.

less stable chair conformation

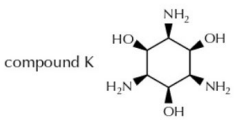
more stable chair conformation

(b) There are additional gauche interactions possible between the OH and $N(CH_3)_2$ substituent groups. Do these interactions disproportionately favor the less stable conformation, the more stable one, or neither? Explain.

(c) Both conformations have 1,3-diaxial interactions. Do the 1,3-diaxial interactions in the more stable comformation disproportionately favor it, disfavor it, or neither, relative to the less stable one? Explain.

(d) Both conformations have 1,3-diaxial interactions. Do the 1,3-diaxial interactions in the less stable comformation disproportionately favor it, disfavor it, or neither, relative to the more stable one? Explain.

(e) Another one of the structures studied was compound K. Is the difference in energy between the two chair conformations of compound K more likely equal to 0.5, 16, 20, or 35.5 kcal/mol? Select and explain.



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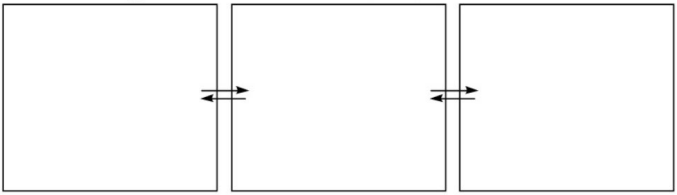
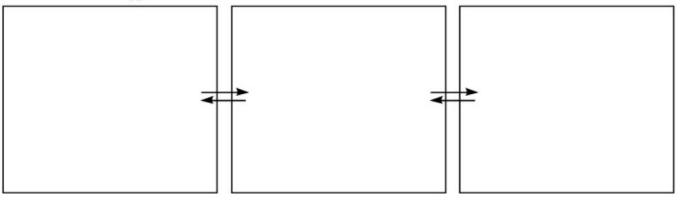
6.33 The conformational behaviors of *meso*-(2*R*, 3*S*)-2,3-dichlorobutane and the racemic 2,3-dichlorobutane have been studied in detail.

In one case, the equilibrium ratio of the three staggered conformations is 98:1:1, with the highest barrier to rotation (activation energy) equal to 12.5 kcal/mol. In the other case, the equilibrium ratio of the three staggered conformations is 62:37:1, with the highest barrier to rotation (activation energy) equal to 5.5 kcal/mol.

(a) Draw the three staggered conformations for *meso*-(2*R*, 3*S*)-2,3-dichlorobutane.



(b) Draw the three staggered conformations for one of the enantiomers: (2*R*, 3*R*)-2,3-dichlorobutane.



(c) In the spaces above, decide which molecule has the 98:1:1 ratio, which has the 62:37:1 ratio, and assign which conformation has which percentage.

(d) Analyze and predict which molecule has the 12.5 kcal/mol as its highest rotational barrier and which one has the lower 9.5 kcal/mol barrier. Use words and drawings to support the prediction.

(e) If you changed the methyl groups to phenyl groups, that is, if the molecules were *meso*-(1*R*, 2*S*)-1,2-dichloro-1,2-diphenylethane and (1*R*, 2*R*)-1,2-dichloro-1,2-diphenylethane, predict how the conformational ratios would change in both cases.

meso-(2*R*, 3*S*)-2,3-dichlorobutane to *meso*-(1*R*, 2*S*)-1,2-dichloro-1,2-diphenylethane	(2*R*, 3*R*)-2,3-dichlorobutane to (1*R*, 2*R*)-1,2-dichloro-1,2-diphenylethane

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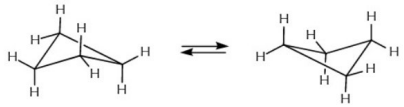
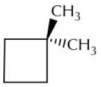
6.34 The two butterfly conformations for cyclobutane were shown in the chapter and they are reproduced here.



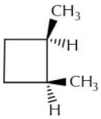
$\Delta G^\circ = 0$
$K_{EQ} = 1$
$E_{ACT} \sim +1.5$ kcal/mol

Including structural and stereoisomers, there are six different dimethylcyclobutanes. For these five of them:
(i) provide the two butterfly conformations
(ii) decide if the ΔG° for the conformational change, as written, is < 0, $= 0$, or > 0
(iii) classify the conformations as identical, enantiomeric, or diastereomeric

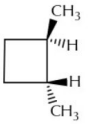
(a)



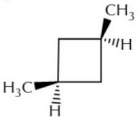
(b)



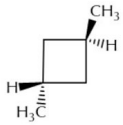
(c)



(d)



(e)



ΔG° for the conformational change, as written, is:
< 0
$= 0$
> 0 kcal/mol

the conformations are:
identical
enantiomeric
diastereomeric

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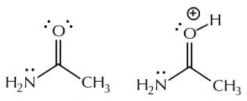
6.35 The CN bond rotation barrier in acetamide is typical for amides, with an experimental value of 15.4 kcal/mol.

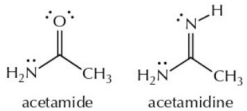
(a) Explain why the bond rotation barrier for the conjugate acid of acetamide is significantly higher, with a calculated value of 30.3 kcal/mol?



acetamide — CN bond rotation E_{ACT} 15.4 kcal/mol

acetamide (conjugate acid) — CN bond rotation E_{ACT} 30.3 kcal/mol

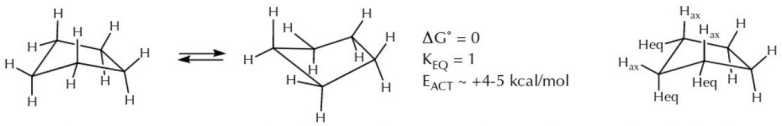
(b) The uncharged version of the conjugate acid of acetamide is called acetamidine, and the comparable bond rotation is significantly lower than in acetamide, with a calculated value of 9.4 kcal/mol. Explain this.



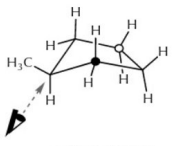
acetamide — CN bond rotation E_{ACT} 15.4 kcal/mol

acetamidine — CN bond rotation (comparable bond) E_{ACT} 9.4 kcal/mol

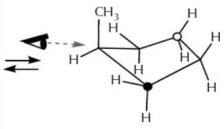
6.36 The conformational analysis for 5-membered rings shares many features with their 4- and 6-membered counterparts. The two pseudoperspective drawings for cyclopentane are shown here. These are referred to as the envelope conformations of cyclopentane. The cyclopentane molecule is not as rigid as cyclohexane, and the single vertex that is out of the plane of the ring is constantly wiggling around the perimeter. At any given moment, however, the three sets of hydrogens at those three vertices are adopting positions referred to as pseudoaxial (H_{ax}) and pseudoequatorial (H_{eq}).



(a) Provide the Newman projections for these two cyclopentane envelope conformations for methylcyclopentane, as indicated by the "eye" perspective. The conformation for this bond is approximately staggered.



conformation A



conformation B

(b) The energy difference between these two forms is 3.5 kcal/mol. Which one is more stable, and why?

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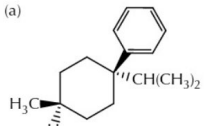
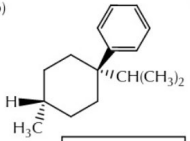
6.37 The table of A-Values can be used to estimate the difference in energy between the two chair conformations in these molecules. Draw the two chair forms and then estimate the ΔG° for the equilibrium, as you have drawn it.

(a)



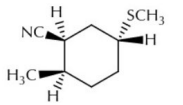
$\Delta G^\circ =$

(b)



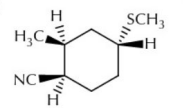
$\Delta G^\circ =$

(c)



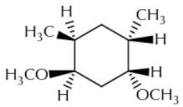
$\Delta G^\circ =$

(d)



$\Delta G^\circ =$

(e)



$\Delta G^\circ =$

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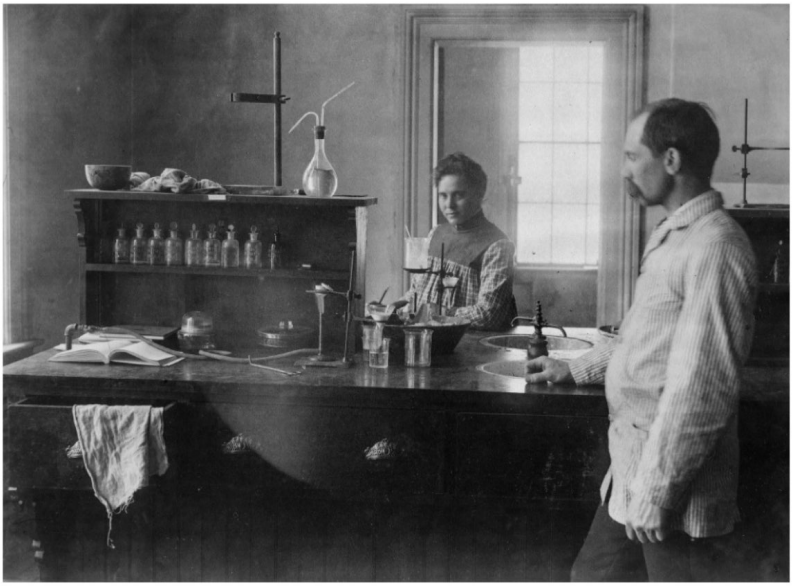

Allen Lysander Colton and Miss Conlin in the Chemistry Laboratory, February 1888.

Chemical History at the University of Michigan

By 1874, the number of laboratory tables for teaching had increased from the original 26, built in 1956, to 190, finally growing to 362 in 1901. Dedicated research space was also available. With its multiple additions over a 50-year period, the building was described by its users as "unhandy" as it was built over time as an incoherent patchwork of spaces. And it was not fireproof. Numerous fires that started up during teaching blowpipe analysis (flame ionization used in chemical identification) resulted in a ruling by the Regents to prohibit its instruction.

One of the faculty commented: "Lack of adequate ventilation in the old building was apparent, especially in late afternoon hours, when dense and acrid fumes dimmed the analytical laboratories, and, incidentally, permitted only a short span of life to the woodwork of fume-closets. Still another serious deficiency was the almost complete lack of sanitary facilities."

Challenges to undergraduate teaching are certainly not a new phenomenon, either. The largest lecture room accommodated about 120, while the classes enrolled nearly 300. The single lecture needed to be offered three times a week, but they were unable to coordinate the quiz sections with the available lecture times. As a result, some students would be quizzed on demonstrations that they had not yet seen.

Public domain image from the Allen Lysander Colton Collection, kindly provided by the Bentley Historical Library (File HS3517).

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CHAPTERS 4–6

Exam Questions

The first midterm examination in the first-term organic chemistry course at the University of Michigan typically has five pages of questions that integrate the topics from Chapters 1–3.

The following pages of "Exam Questions" (EQ 02.01–EQ 02.30) were used in examinations between 1998–2019.

The 5-page examinations are laid out for a 60-minute time period, and students have 90 minutes to take the tests.

Any set of five pages from this group of 30 questions might be used to create a practice exam.

Select any five of these pages and time yourself for 90 minutes, without accessing any resources, to self-test your mastery of the main topics from Chapters 4–6.

Chapter 4

- Classifying organic reactions
  - Complexation-decomplexation reaction
  - Substitution reactions
  - Addition reactions
  - Elimination reactions
- Reaction energy diagrams
- Electrophilic addition reactions of strong Brønsted acids to pi bonds
- Electrophilic addition reactions of weak Brønsted acids to pi bonds

Chapter 5

- Naming organic compounds
  - Alkanes, cycloalkanes, alkenes, alkynes
  - Alcohol, alkyl halides
- Molecular symmetry and Nuclear Magnetic Resonance spectroscopy
- Sources of stereoisomerism
  - Double bonds that are unsymmetrically substituted at both ends
  - Symmetrical, even-number rings that are substituted at opposite vertices
  - Tetrahedral atoms with four different substituents
- Chirality and optical activity in molecules with a single source of stereoisomerism
- Chirality and optical activity in molecules with multiple sources of stereoisomerism

Chapter 6

- Conformational analysis involving bond rotations using two sp^3 atoms
- Conformational analysis involving partial bond rotations in small rings
- Stereoisomerism and fluxional behavior involving heteroatoms and double bonds

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EQ 02.01

HEADLINE - PNC Professor Finds That MTBE Additive Threatens Drinking Water in States Where it is Not Routinely Used

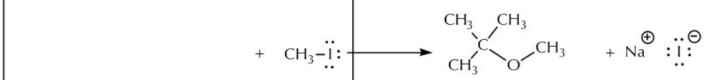
WESTVILLE - An ongoing survey of gas stations in the Midwest reveals that MTBE, a common gasoline additive, is present in sites where it is not routinely used, posing a growing threat to ground water in these areas, according to Reynaldo Barreto, Ph.D., an associate professor at Purdue University North Central in Westville, Ind., and the study's lead investigator. The study was described by Barreto on Aug. 30, 2001, at the 222nd national meeting of the American Chemical Society, the world's largest scientific society, held in Chicago.

http://www.pnc.edu/cd/news/mtbe.html

MTBE is methyl t-butyl ether, $(CH_3)_3COCH_3$, a common (albeit controversial) gasoline additive.

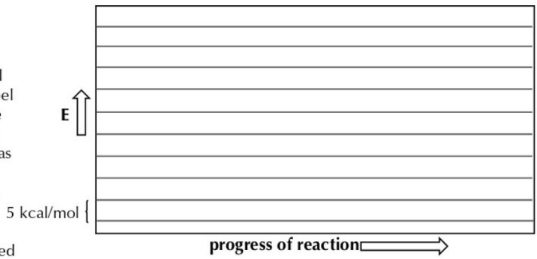
(a) Complete the following reaction, in which MTBE is prepared as a product. You should also provide the curved arrow mechanism for the reaction.

complete this balanced chemical reaction and provide the curved arrow mechanism



methyl t-butyl ether
MTBE

(b) Provide an energy diagram for the formation of MTBE. Include the level of the starting materials (label as "SM"), the products (label as "P"), and any intermediates (label as "I-1," "I-2," etc.), along with the energy curve(s) that relate them to each other. The overall reaction has a ΔG° of -10 kcal/mol, and an activation energy of +25 kcal/mol.



(c) Provide a drawing of the anticipated transition state structure for this reaction. Dashed lines should be used to represent partially forming or breaking bonds, and any partial charges should be indicated. You do not need to show the sodium ion.

(d) How many signals will there be in the ^{1}H-NMR spectrum of MTBE?

(e) What will be the ratio of the size (area) of the ^{1}H-NMR signals?

(f) How many signals will there be in the ^{13}C-NMR spectrum of MTBE?

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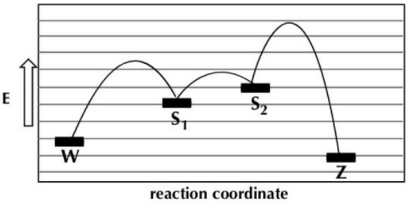
EQ 02.02

A. This energy diagram represents a chemical reaction where the starting material (compound **S**) exists as a mixture of forms ($\mathbf{S_1}$ and $\mathbf{S_2}$) that are in equilibrium. The $\mathbf{S_1}$ form gives one product (compound **W**) while the $\mathbf{S_2}$ form gives another product (compound **Z**).

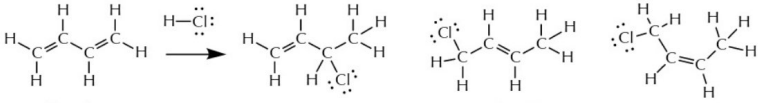


Reversible reactions are indicated with double arrows: ⇄
Irreversible reactions are indicated to be in the direction shown by a single arrow: →

(a) under the following conditions: $\mathbf{W} \leftarrow \mathbf{S_1} \rightleftarrows \mathbf{S_2} \rightarrow \mathbf{Z}$ Which product predominates?

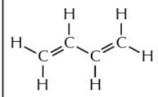
(b) under the following conditions: $\mathbf{W} \rightleftarrows \mathbf{S_1} \rightleftarrows \mathbf{S_2} \rightleftarrows \mathbf{Z}$ Which product predominates?

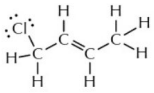
B. The electrophilic addition of HCl to 1,3-butadiene gives a mixture of three products:



1,3-butadiene — product **P** — product **Q** — product **R**

(a) Provide the complete, stepwise, curved arrow mechanism for the formation of product **Q**.





product **Q**

(b) What is the stereoisomeric relationship between products **Q** and **R**?

(c) What is the stereochemical configuration of product **Q**?

(d) How many optically active stereoisomers are there for product **P**?

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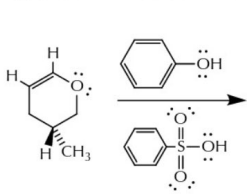
EQ 02.03

A. The reaction shown below gives a mixture of diastereomers as the major products.

(a) Draw the structures for these two diastereomeric products.

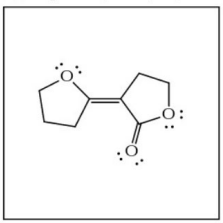


benzenesulfonic acid
(catalyst)

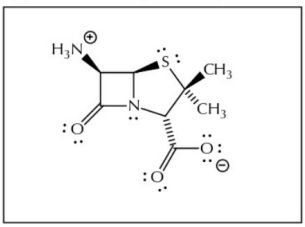
(b) As an acid-catalyzed electrophilic addition reaction, the first significant mechanistic step in this reaction involves combining the nucleophilic alkene with the Brønsted acid in highest concentration to give preferentially the reactive intermediate that forms faster. Draw the structures of the molecules involved *in this step* (only), the curved arrow mechanism that illustrates the expected reaction, and the structure of the reactive intermediate (in the event that the reactive intermediate has more than one resonance contributor, the most significant contributor to its structure should be shown). Note that you are only being asked to show the one step, not the entire mechanism.

B. Circle the appropriate atom or grouping of atoms for which a stereochemical label can be assigned, and clearly point to and provide the corresponding label (*R*, *S*, *E*, *Z*). If there is no label needed for any part of the molecule, write "none" in the box.

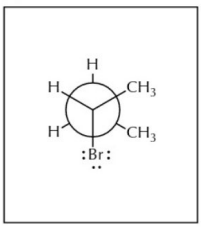
(a) *J Org Chem*, **2003**, *68*, 9742



(b) penicillinic acid (from mold)



(c) 2-bromobutane



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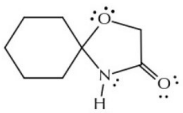
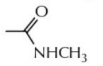
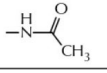
EQ 02.04

A. The specific A-Values needed for compound X are not known, but two of the groups listed here are adequate for estimating the direction of the equlibrium between its two chair forms.



compound X

Group	A-Value
$-OCH_3$	0.67
$-CH_2OCH_3$	1.70
	1.35
	1.1

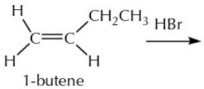
Draw the two chair conformations for compound X. The chair drawing should clearly represent the chair-to-chair interconversion. You need only show the substituents used in the drawing for compound X (in other words, none of the ring hydrogen atoms needs to be drawn). The directionality for the connectivity of the substituent groups on the cyclohexane ring must be shown clearly and without ambiguity in order to receive credit. The drawings should be placed in the answer spaces so that the equilibrium constant is greater than 1 (K_{EQ} = [Form P]/[Form Q]).

Form Q

Form P

B. When hydrobromic acid (HBr) is added to 1-butene (see below), a mixture of electrophilic addition reaction products is expected. In fact, when you account for the formation of stereoisomers, there are 3 products: the major products are a racemic mixture, and the minor product is a single, achiral molecule.

(a) Draw these three different molecules in the spaces, as directed.



1-butene

one of the racemic pair + one of the racemic pair + the single, achiral product

(b) When 1-butene and HBr are heated at high temperatures, a completely unexpected C_4H_9Br constitutional isomer is observed. Its ^{1}H-NMR spectrum shows only one group of hydrogen atoms and its ^{13}C-NMR shows only 2 groups of carbon atoms. Based on these data, what is the structure of this molecule?

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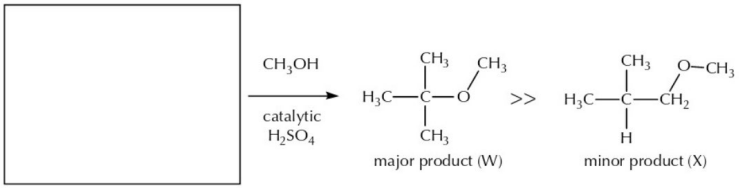
EQ 02.05

A. (a) Complete the following electrophilic addition reaction by providing the starting material that is necessary to carry out this transformation.



(b) The major (W) and minor (X) products can be easily separated and have their properties determined, including ^{1}H-NMR and ^{13}C-NMR.

How many groups of each kind of atom would be observed in the ^{1}H-NMR and ^{13}C-NMR spectra for these two molecules?

	^{1}H-NMR	^{13}C-NMR
major product (W)		
minor product (X)		

(c) Provide the Newman projections for three staggered conformations for the minor product (X), for the C-C bond between the "CH" and the "CH_2." Use the point of view with the carbon of the "CH_2" as the front atom, and the carbon of the "CH" as the back atom.

Form T	Form U	Form V

(d) Complete the following statements about the relative stabilities of Forms T, U, and V. You can only receive credit for this if the three staggered conformations in part (c) are correct.

Form T is (*circle one*) { more stable than / less stable than / the same stability as } Form U, which is (*circle one*) { more stable than / less stable than / the same stability as } Form V.

If each of the gauche interactions in the most stable conformation is worth 0.35 kcal/mol, then the anticipated energy difference between the most stable and least stable staggered conformation is what value? (*select one*)

- ☐ less than 0.30 kcal/mol
- ☐ exactly 0.35 kcal/mol
- ☐ between 0.40 and 0.65 kcal/mol
- ☐ exactly 0.70 kcal/mol
- ☐ greater than 0.75 kcal/mol

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EQ 02.06

A. Many organic molecules have been identified in a distant molecular cloud using spectroscopic methods, including all of the structural isomers of C_3H_6O. Only one of these isomers exists as a pair of enantiomers, and their discovery in interstellar space is potentially part of the interesting story about why we usually see only one enantiomer in naturally occuring substances. Draw the (*R*)-stereoisomer of the chiral C_3H_6O isomer (all atoms uncharged and closed shell).

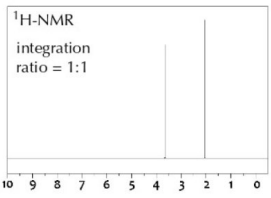
C_3H_6O

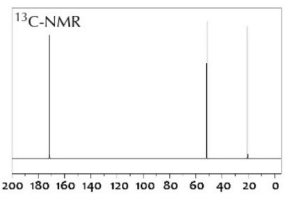
"The observations presented here were taken toward the Sagittarius B2 North molecular cloud, the preeminent source for new complex-molecular detections in the interstellar medium."

Science, **2016**, *352*, 1449.

26,000 light years from earth
150 light years across
390 light years from the galactic center

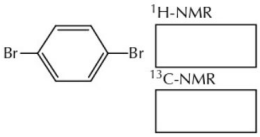
B. About 150 different organic molecules have been detected in interstellar space. The ^{1}H-NMR and ^{13}C-NMR spectra for a $C_3H_6O_2$ molecule are shown below. What is its structure?

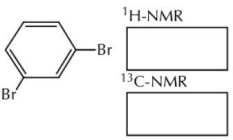


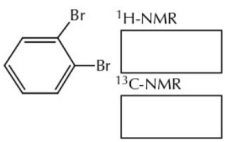


$C_3H_6O_2$

C. How many signals would you expect in the hydrogen and carbon NMR spectra for the follow three isomers?







D. (a) Draw (1*R*, 2*S*)-1-bromo-2-chlorocyclobutane

(b) What is the stereochemical relationship between the two butterfly conformations for this molecule? (*select one*)

- ☐ identical
- ☐ enantiomeric
- ☐ diastereomeric

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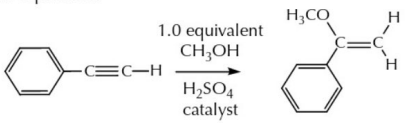
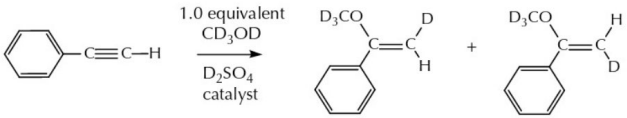
EQ 02.07

The electrophilic addition reaction of methanol (CH_3OH) to the triple bond in the molecule shown below can be controlled to result in the addition of just 1.0 equivalent.

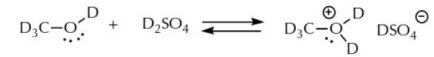
As a way to study the mechanism of this reaction, the deuterium versions of methanol (CD_3OD) and sulfuric acid (D_2SO_4) were used. This results in a mixture of stereoisomers, as shown below:



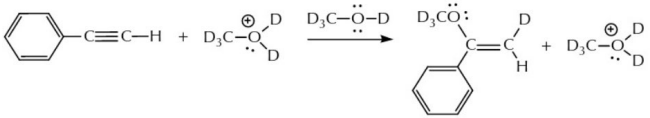


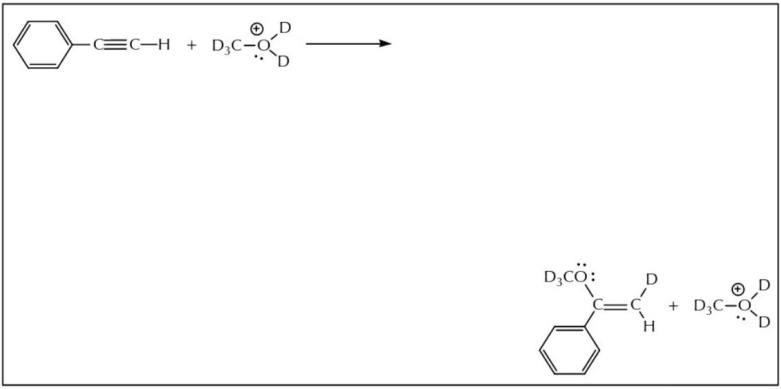
NOTES:

(1) chemically, deuterium (D, ^2H) behaves exactly the same way as protium (H, ^1H)
(2) accordingly, the available acid is derived from CD_3OD reacting with D_2SO_4:



(a) Provide the complete, stepwise curved arrow mechanism for this balanced equation. Include all features, such as nonbonding electron pairs and formal charges, as well as the regeneration of the acid, as shown below.





(b) What is the appropriate stereochemical label to describe the geometry of the product?

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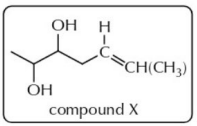
EQ 02.08

A. Answer the following questions as directed.



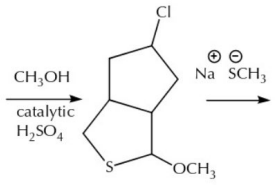
compound X

(a) Draw the stereoisomer of compound X that has its two stereocenters in the "S" configuration, and its double bond in the "E" configuration.

(b) What are the three configurational labels for the enantiomer of this "(*S*, *S*, *E*)" stereoisomer of compound X?

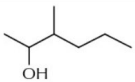
(c) Complete the following reaction sequence based on the provided information.

C_7H_9ClS



B. When the following molecule (W: $C_7H_{16}O$) is treated at 90°C with aqueous phosphoric acid, an new structural isomer (Y) is formed. Not only does compound Y retain the $C_7H_{16}O$ molecular formula, but it also still retains an alcohol group (OH). The NMR spectra for compound Y are shown here. From these data, deduce the structure of compound Y.

IMPORTANT NOTE: You are not meant to be able to figure out the product from the chemistry. This particular reaction is unusual in that it results in a substantial reorganization of the connectivity of the carbon atoms. Use the experimental data!

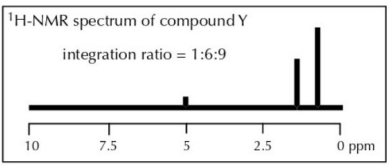


compound W

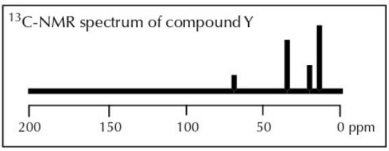
aqueous
H_3PO_4
90°C

compound Y
$C_7H_{16}O$
retains an OH group
NMR spectra shown below

^{1}H-NMR spectrum of compound Y



^{13}C-NMR spectrum of compound Y



structure for compound Y

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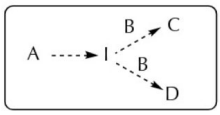
EQ 02.09

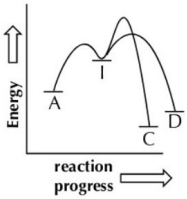
A. In the following hypothetical reaction, the starting material (A) is converted to a reactive intermediate (I). Intermediate I then reacts with compound B to give the observed products C and D.



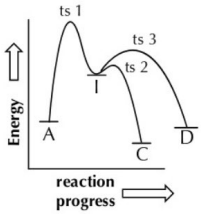
"ts" = transition state

Two possible energy diagrams for this reaction are shown here.

energy diagram I



energy diagram II



(a) If all the steps are reversible, and D is observed to be the major product, then which of the Energy Diagrams could be correct?

check one:
I only ☐ both ☐
II only ☐ neither ☐

(b) If all of the steps are irreversible, and C is observed to be the major product, then which of the energy diagrams could be correct?

check one:
I only ☐ both ☐
II only ☐ neither ☐

(c) If increasing the concentration of compound B does not increase the overall reaction rate, which energy diagram is consistent with this information?

check one:
I only ☐ both ☐
II only ☐ neither ☐

With reference to the seven identifiable points in Energy Diagram II (A, I, C, D, ts 1, ts 2, and ts 3), the energy difference between which two of these points...

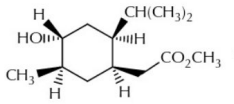
(d) ... determines the equilibrium constant for the A to I interconversion if all steps are reversible?

check two:
A ☐ I ☐ C ☐ D ☐
ts 1 ☐ ts 2 ☐ ts 3 ☐

(e) ... influences the overall rate of the A to D conversion if D forms irreversibly?

check two:
A ☐ I ☐ C ☐ D ☐
ts 1 ☐ ts 2 ☐ ts 3 ☐

B. Compound G is an unnatural derivative of a natural substance known as carvone (*J Braz Chem Soc*, **2006**, *17*, 4778). In the space below, using this data table for the A-Values, draw the more stable chair conformation for compound G.



compound G

Group	A-Value
-OH	0.87
$-CO_2CH_3$	1.29
$-CH_2OH$	1.75
$-CH_3$	1.7
$-CH_2CO_2CH_3$	1.9
$-CH(CH_3)_2$	2.15
$-C(CH_3)_3$	4.5

How many of the following additional interactions are there in this conformation?

gauche interactions between 2 substitutents? ☐

1,3-diaxial interactions between 2 substituents? ☐

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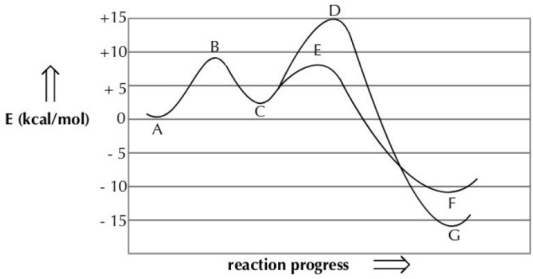
EQ 02.10

A. Compound A reacts to give two products F and G. The energy diagram for a particular example of a chemical reaction meeting these criteria was published (*J Org Chem*, **2000**, *65*, 6601).



Energy relative to A
B + 9.3 kcal/mol
C + 3.0 kcal/mol
D + 15.0 kcal/mol
E + 7.9 kcal/mol
F - 13.2 kcal/mol
G - 16.6 kcal/mol

Answer the following questions concerning this energy diagram. Place the letter, letters, or numerical values corresponding to the answer(s) in the answer spaces.

(i) Which point(s) on the diagram correspond to transition state(s)? i

(ii) Which step in the forward reaction for the transformation of A to G is the rate-determining step? ii ____ to ____

(iii) If the formation of F and G are reversible, which product will dominate at equilibrium? iii

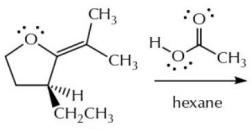
(iv) What is the value (kcal/mol) of the activation energy for the C to F step? iv

(v) What is the value (kcal/mol) of the ΔG° for the formation of the most stable product (for the complete reaction, starting from A)? v

(vi) If the formation of F and G are both irreversible, which product will dominate? vi

B. The electrophilic addition reaction of acetic acid to compound M gives a mixture of stereoisomeric products via a common reactive intermediate.

(a) Provide the two stereoisomeric products predicted to result from this reaction.



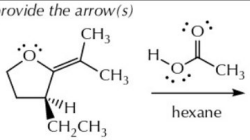
compound M

+

(b) What is the stereoisomeric relationship between these two products?

(c) Provide the reactive intermediate and the curved arrow mechanism for its formation.

provide the arrow(s) *provide the balanced equation*



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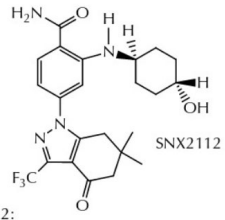
EQ 02.11

Neglected tropical diseases (NTDs) represent an undeniable threat to human health (*Med Chem Lett*, **2017**, *8*, 797). The World Health Organization has prioritized 17 diseases that affect more than 1.5 billion people around the world, the vast majority of whom are impoverished. One of these diseases is leishmaniasis, a parasitic infection transmitted to humans through the bite of phlebotomine sandflies, with an estimated 12 million people currently infected. SNX2112 is being investigated for its potential therapeutic activity.



SNX2112

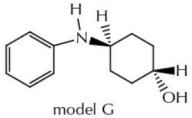
(a) Answer the following questions about this specific isomer of SNX2112:

(i) How many optically active diastereomers does it have?

(ii) How many optically inactive diastereomers does it have?

(iii) How many optically active enantiomers does it have?

(b) The following molecule (model G) might be used to study the conformational analysis of SNX2112. Given the following data, draw the most stable chair conformation for model G — show clearly the positions for the -NHPh and -OH substituents, as well as the hydrogen atoms on the carbons to which they are attached.



model G

group	A-Value
-NHPh	+ 1.47
-OH	+ 0.87

more stable chair conformation of model G

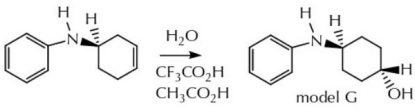
(c) What is the estimated value of the ΔG° (kcalmol^{-1}) for the equilibrium between the less stable chair conformation and this more stable counterpart?

model G

less stable chair $\rightleftharpoons$ more stable chair

ΔG° (kcalmol^{-1})

(d) The addition of water to the following compound can be used to prepare model G. However, there are also three other regio- and/or stereoisomeric products. Of these four products (model G and the three other products), draw one of the compounds that is chiral.



model G

plus 3 other regio- and/or stereoisomer products

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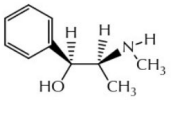
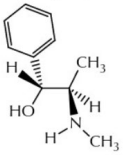
EQ 02.12

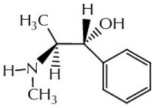
The compounds drawn below are examples of bioactive alkaloids, some of which are used as the major constituents of familiar over-the-counter drugs known as Sudafed, Bronkaid, and Ami-Tex.



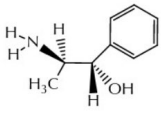
(+)-pseudoephedrine



(-)-pseudoephedrine



(-)-ephedrine

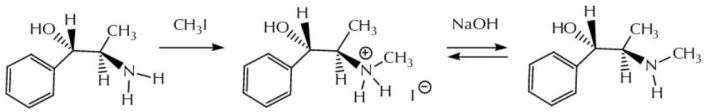


(+)-norephedrine

(a) Answer the following by writing "yes" or "no" or a numeral ("0", "1", "2", etc.) in the spaces.

consider:	are they: diastereomers	enantiomers	constitutional isomers	both optically active	how many stereocenters (total) have the (*R*)- configuration?
(+)-pseudoephedrine & (-)-ephedrine					
(-)-pseudoephedrine & (-)-ephedrine					
(+)-pseudoephedrine & (-)-pseudoephedrine					
(+)-norephedrine & (-)-ephedrine					

The preparation of (+)-ephedrine can be accomplished by the reaction of (+)-norephedrine with iodomethane followed by the deprotonation of the initially formed conjugate acid of (+)-ephedrine, called (+)-ephedrine•HI.



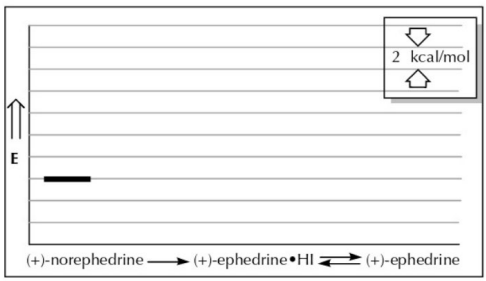
(+)-norephedrine (+)-ephedrine•HI (+)-ephedrine

ΔG° = +8 kcal/mol
Activation E = +14 kcal/mol

ΔG° = -10 kcal/mol
Activation E = +2 kcal/mol

(b) Provide a drawing for the transition state structure of the rate-determining step for the forward reaction. Be sure to include electron pairs and partial charges.

(c) Complete the energy diagram for this reaction.



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EQ 02.13

A. Two different structural (constitutional) isomers (A and B) of C_3H_4 give the same product (C) from the sulfuric acid-catalyzed electrophilic addition reaction of methanol (CH_3OH) (see, e.g., *J Org Chem*, **1981**, *46*, 2683). Given this information, in addition to the ^{1}H-NMR and ^{13}C-NMR spectral data, below, what are the structures of A, B, and C?

A: C_3H_4
2 ^{13}C-NMR signals; 1 ^{1}H-NMR signal

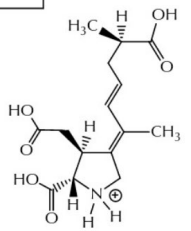
B: C_3H_4
3 ^{13}C-NMR signals; 2 ^{1}H-NMR signals (3:1 ratio)

excess CH_3OH
catalytic H_2SO_4

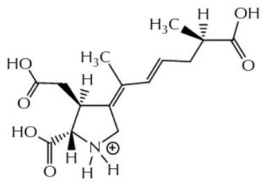
C: $C_5H_{12}O_2$
3 ^{13}C-NMR signals;
2 ^{1}H-NMR signals (1:1 ratio)

B. Isodomoic acids G and H are naturally occurring marine compounds. They are derived from domoic acid, which is the toxin responsible for several outbreaks of poisoning associated with the consumption of contaminated mussels (*J Am Chem Soc*, **2009**, *131*, 17714).

Answer the following questions about isodomoic acids G and H.



isodomoic acid G



isodomoic acid H

(a) Which of the following terms apply to isodomoic acids G and H? Mark all that apply with an "X". No partial credit.

- ☐ acids G & H are enantiomers
- ☐ acids G & H are diastereomers
- ☐ acids G & H are constitutional isomers
- ☐ acids G & H are stereoisomers

(b) Which of the following are true? Mark all that are true with an "X". No partial credit.

- ☐ acid G has two (*E*) double bonds
- ☐ acid H has only one (*S*) stereocenter
- ☐ a 1:1 mixture of acids G & H is optically inactive
- ☐ acids G & H are both optically active

(c) Draw the major form of isodomoic acid H at pH = 8.

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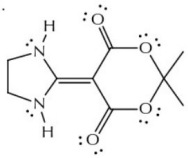
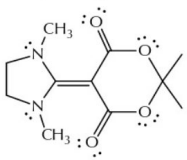
EQ 02.14

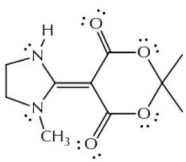
A. The carbon-carbon double bonds in the following three compounds have rotational barriers of 3.6, 6.6, and 17.1 kcal/mol, which means that two of them are freely rotating at room temperature, while the third one is rotating slowly, if at all.



compound HH



compound MM



compound HM

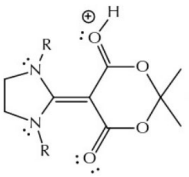
(a) Predict which carbon-carbon bond rotational barrier (kcal/mol) is associated with which compound. Place an "X" in the box corresponding to the proper value for that compound.

	3.6	6.6	17.1
compound HH			
compound MM			
compound HM			

(b) The bond with the lowest barrier (3.6 kcal/mol) is experiencing destabilization in the form that maintains the double bond. Classify the source of destabilization as a type of interaction and provide the structural description of where this interaction arises from in the molecule. Be sure you are talking about the molecule you selected for the 3.6 kcal/mol barrier.

(c) On the other hand, the bond with the highest barrier (17.1 kcal/mol) is experiencing stabilization in the form that maintains the double bond. Classify the source of stabilization as a type of interaction and draw the molecule with a depiction of the interaction. Be sure you are talking about the molecule you selected for the 17.1 kcal/mol barrier.

(d) In all three cases, the conjugate acids, resulting from protonation at the oxygen atom of the C=O, have carbon-carbon bond rotational barriers that are lowered (i.e., decreased activation energy for the bond rotation). Provide a single, all closed shell atom resonance contributor that explains the lower bond rotational energy.



R = H, CH_3

Briefly state why this resonance contributor is consistent with a lower rotational energy for the carbon-carbon double bond.

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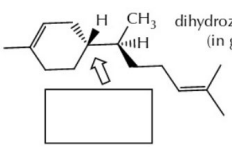
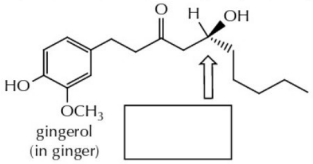
EQ 02.15

A. Assign the stereochemical labels to the indicated atoms in the following two compounds, which are found in the so-called "pumpkin spice" that flavors everything from lattes to toothpaste, and which has more to do with spices than it does with pumpkins, being a toasted up mixture of mainly cinnamon, clove, nutmeg, allspice, and ginger.

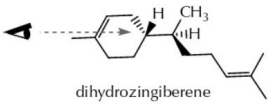


dihydrozingiberene (in ginger)



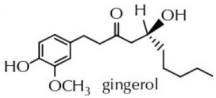
gingerol (in ginger)

B. Provide the Newman projection for the bond in dihydrozingiberene with the two stereocenters, which is already drawn in its most stable conformation, from the perspective indicated here (stereocenter on the left = front, right = back).



dihydrozingiberene

C.

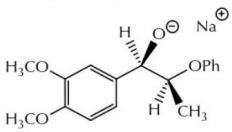


gingerol

i. The specific stereoisomer of gingerol, shown here, has how many optically active diastereomers?

ii. The specific stereoisomer of gingerol, shown here, has how many optically active enantiomers?

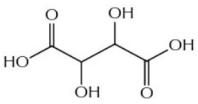
D. Draw the product (preparation of a new medicine derived from nutmeg [*Med Chem Lett*, **2017**, *8*, 715]).



CH_3CH_2Br →

+ NaBr

E. An online recipe for sourdough pumpkin spice scones uses homemade pumpkin spice and "cream of tartar," which is derived from tartaric acid, and which has a *meso* stereoisomer. Draw the *meso* stereoisomer of tartaric acid (connectivity shown here).



tartaric acid

meso-tartaric acid

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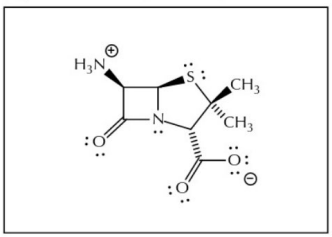
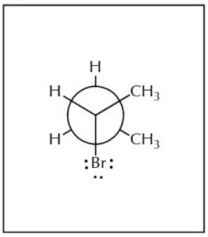
EQ 02.16

A. Circle the appropriate atom or grouping of atoms for which a stereochemical label can be assigned, and clearly point to and provide the corresponding label (*R*, *S*, *E*, *Z*, *cis*, *trans*).

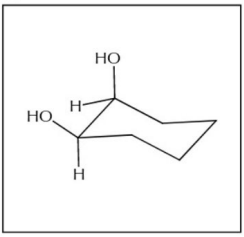
(a) penicillinic acid (from mold)



(b)

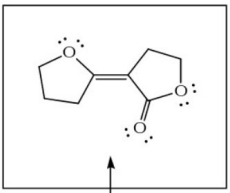


(c)



B. *J Org Chem*, **2003**, *68*, 9742.

Draw the all closed shell atom resonance contributor that explains why the carbon-carbon double bond rotational barrier is low, then show the structure of the diastereomer of the original molecule with which it is in equilibrium because of that bond rotation.

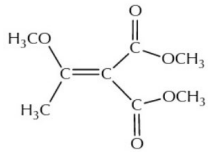


draw the most significant resonance contributor of the diastereomer

C. The rotational activation energies for the carbon-carbon double bonds in the following pair of compounds have been measured and the values are reported below. Provide an explanation for the difference.

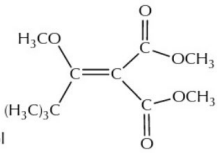
compound A

E_A for C=C bond rotation = 25.7 kcal/mol



compound B

E_A for C=C bond rotation = 18.3 kcal/mol



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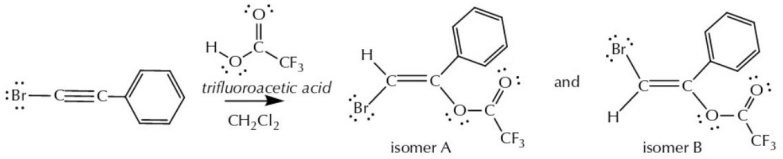
EQ 02.17

Molecules with carbon-carbon triple bonds are routinely used as building blocks for the preparation of more complex organic compounds. In the following reaction, the addition of one equivalent of trifluoroacetic acid (pK_a -0.3), in an inert solvent (CH_2Cl_2), is proposed to take place with a high degree of regioselectivity and giving mainly one of the two possible diastereomeric products (*Org Lett*, **2016**, *18*, 4770).



(a) The observed A:B ratio is at least 30:1 (A > B). What are the stereochemical labels used to distinguish the difference between diastereomers A and B?

Label for isomer A

Label for isomer B

(b) Provide the curved arrow mechanism for the first step (only) of the reaction that leads to the formation of the major product (isomer A). Include both of the relevant starting materials, the curved arrows, and the structure of the resulting intermediate (including nonbonding electrons, charges, etc.)

relevant starting materials and curved arrows for the first step

structure of the intermediate leading to A (including the anticipated geometry)

(c) Using dotted lines to represent partial bonds and including all structural features including partial charges and nonbonding electrons, draw the anticipated transition state structure for the reaction step asked for in part (b), that is, the first step in the mechanism that leads to the formation of isomer A.

(d) A small amount of the regiosiomeric addition product is observed (also formed as two diastereomers). Of these two, the major one is the one with the (Z) configuration. Draw the structure for the regiosomeric product to isomers A and B that has the (Z) configuration.

(e) Explain the regioselectivity observed in the formation of isomers A and B (collectively, not the A:B ratio) relative to the other regioisomer. Use words and structural drawings as necessary to make your point.

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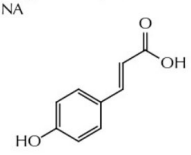
EQ 02.18

Analyze the structures of each of the following compounds. First assign stereochemical label(s) to any sources of stereoisomerism in the molecule. Then answer the questions that refer to the specific molecule shown.

A. (a) Identify all sources of stereoisomerism and label the geometries; if there are none, write NA

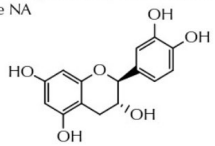


one of the coumaric acids

(b)

(i) Is this specific molecule optically active?	
(ii) How many diastereomers does this specific molecule have?	
(iii) How many of this compound's stereoisomers (including this one) are chiral?	
(iv) How many ^{1}H-NMR signals would its spectrum show?	
(v) How many ^{13}C-NMR signals would its spectrum show?	
(vi) Estimate the pK_a for the most acidic proton on this compound	

B. (a) Identify all sources of stereoisomerism and label the geometries; if there are none, write NA

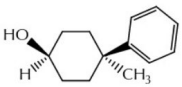


(–)-catechin - a flavenoid isolated from tannic juice

(b)

(i) How many enantiomers does this specific molecule have?	
(ii) How many diastereomers does this specific molecule have?	
(iii) How many of this compound's stereoisomers (including this one) are chiral?	
(iv) Is this specific molecule dextrorotatory?	
(v) How many ^{13}C-NMR signals would its spectrum show?	
(vi) Estimate the pK_a for the most acidic proton on this compound	

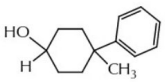
C. (a) Identify all sources of stereoisomerism and label the geometries; if there are none, write NA



(b)

(i) How many enantiomers does this specific molecule have?	
(ii) How many diastereomers does this specific molecule have?	
(iii) How many of this compound's stereoisomers (including this one) are chiral?	
(iv) How many ^{13}C-NMR signals would its spectrum show?	

(c) Give the IUPAC name for this compound (connectivity only).



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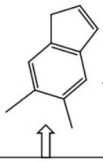
EQ 02.19

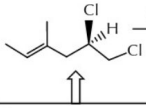
Analyze the starting materials for these reactions as requested. Each of the following reactions yields only a pair of isomeric compounds. Assume that any regioselectivity is 100% selective, and consider the possibility of stereoisomeric products when drawing each of these products. Clearly show connectivity and stereochemistry as necessary to define them as unique compounds.

A.



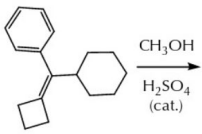
(a) Draw the two different products +	(b) The relationship between these two products is (*circle one*): enantiomers diastereomers structural isomers
(c) How many ^{13}C-NMR signals?	(d) Describe the optical activity of these two products (*circle one*): both are optically active; both are optically inactive; one is optically active and the other is not

B.



(a) Draw the two different products +	(b) The relationship between these two products is (*circle one*): enantiomers diastereomers structural isomers
(c) How many ^{13}C-NMR signals?	(d) Describe the optical activity of these two products (*circle one*): both are optically active; both are optically inactive; one is optically active and the other is not
(e) Give the complete IUPAC name for this starting material (including stereochemical labels)	

C.



(a) Draw the two different products +	(b) The relationship between these two products is (*circle one*): enantiomers diastereomers structural isomers
(c) Describe the optical activity of these two products (*circle one*): both are optically active; both are optically inactive; one is optically active and the other is not	

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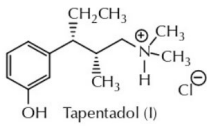
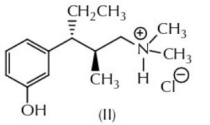
EQ 02.20

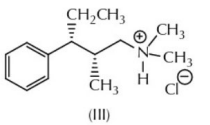
A. Tapentadol (compound I) is a centrally acting analgesic (painkiller) with a unique profile of action. Due to the potential importance of compound I as a pharmaceutical drug, some of the related compounds (i.e., II - VI) have been prepared, characterized, and studied (*Act Crystallogr C*, **2011**, *67*, 71).



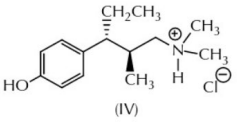
Tapentadol (I)



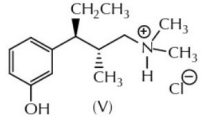
(II)



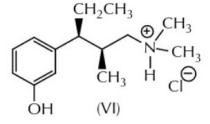
(III)



(IV)



(V)

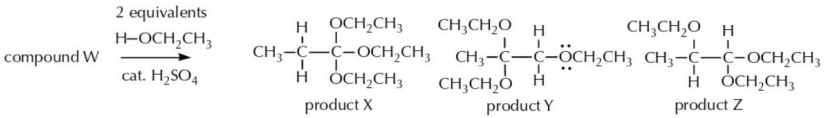


(VI)

Complete the following table about the relationship between some of these compounds.

		they are: diastereomers	enantiomers	each one has both an (*R*)- and an (*S*)- stereocenter
(i)	compounds I and II (write "yes" or "no")		■	
(ii)	compounds I and VI (write "yes" or "no")	■		
(iii)	compounds II and IV (write "yes" or "no")		■	■
(iv)	compounds II and V (write "yes" or "no")	■		■

B. The following electrophilic addition reaction could result in three different products (X, Y, and Z).



(a) NMR spectroscopy can be used to differentiate these three outcomes. For each of these products, tell (i) how many C atom signals would be observed in the ^{13}C-NMR, (ii) how many H atom signals would be observed in the ^{1}H-NMR, and (iii) what the area ratio of the H atom signals would be (any order).

	#C signals	#H signals	ratio of H signals
product X			
product Y			
product Z			

(b) Compound W exhibits the following data:

Molecular formula: C_5H_8O
^{1}H-NMR: 3 signals (3:3:2 ratio)
^{13}C-NMR: 5 signals

Using the information from the chemistry (above) and the data given here, what is the structure of compound W?

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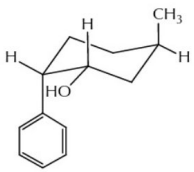
EQ 02.21

Various forms of molecular motion fall under the heading of fluxional behavior where, under normal experimental conditions, the molecular geometries cannot be isolated and stored as stable substances. In the following cases, draw the other major geometry (or geometry as directed) that is in equilibrium with the one that is shown. Answer the appended questions.

(a)



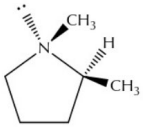
the other chair form

(i) the two conformations are:
- ☐ enantiomeric
- ☐ diastereomeric
- ☐ identical

(ii) the ΔG° (as written) is:
- ☐ > 0
- ☐ = 0
- ☐ < 0

(iii) the stereochemical label for the carbon 1: ☐

(b)



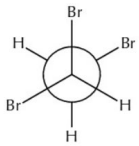
the nitrogen inversion

(i) the two forms are:
- ☐ enantiomeric
- ☐ diastereomeric
- ☐ identical

(ii) the stereochemical label for the nitrogen atom in the original: ☐

(iii) overall, the molecule is
- ☐ chiral
- ☐ achiral

(c)



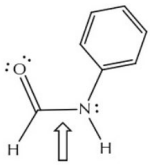
rotate the front carbon counterclockwise by 120° (i.e., -120°)

(i) the two forms are:
- ☐ enantiomeric
- ☐ diastereomeric
- ☐ identical

(ii) the ΔG° (as written) is:
- ☐ > 0
- ☐ = 0
- ☐ < 0

(iii) the number of gauche interactions in the original: ☐

(d)



carbon-nitrogen bond rotation

(i) the two forms are:
- ☐ enantiomeric
- ☐ diastereomeric
- ☐ identical

(ii) the ΔG° (as written) is:
- ☐ > 0
- ☐ = 0
- ☐ < 0

(iii) the stereochemical label for the original CN bond: ☐

recall what the effect of resonance will be on the conformations of the indicated bond

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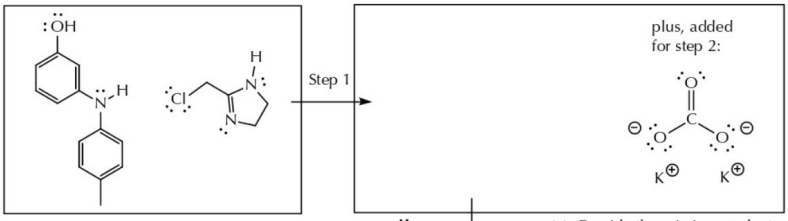
EQ 02.22

Follow the relatively simple two-step synthesis of the following compound, phentolamine, by providing the curved arrow(s) and all missing structures. Read the descriptions completely before you start your mechanism.

(a) Provide the curved arrow mechanism that leads to the formation of an ionic product.

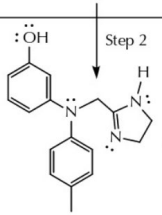
(b) Draw the missing ionic product. Provide the mechanism for the proton transfer that completes this transformation.



The following information has been determined for this transformation

For Step 1: $\Delta G^{\circ}_{step\ 1} = -10$ kcal/mol, $E_{ACT} = 15$ kcal/mol

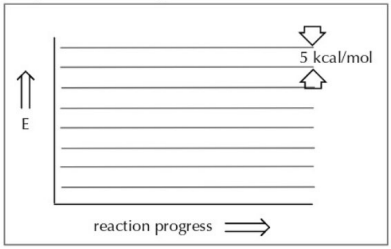
For Step 2: $\Delta G^{\circ}_{step\ 2} = -5$ kcal/mol, $E_{ACT} = 5$ kcal/mol



phentolamine

(c) Provide the missing products (balance your reaction).

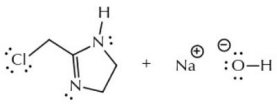
(d) Sketch an energy diagram for this transformation using the information given above.



(e) Which is the rate-determining step for the forward reaction?

(f) What is the overall ΔG° for the reaction?

(g) The base added for step 2, above (K_2CO_3), is relatively weak. The reason for this is that if a strong base is added (such as sodium hydroxide, NaOH), a competing substitution reaction takes place. Draw the transition state for the 1-step substitution reaction predicted to occur with NaOH. Include partial bonds, partial charges, and the nonbonding electron pairs.



Draw the transition state for the 1-step substitution reaction.

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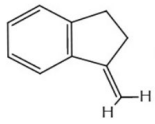
EQ 02.23

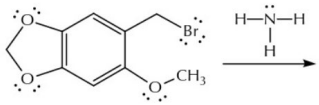
Provide the structures for the compounds that are required to complete the following reactions.

(a)



(R)- stereoisomer of the major regioisomer

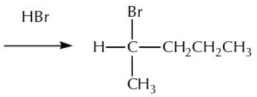
(b)



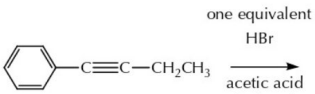
balanced equation for the ionic product

(c)

highly regioselective addition reaction

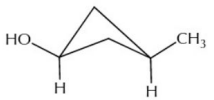


(d)



(Z)-stereoisomer of the major regioisomer

(e)



(i) the stereochemical relationship of other butterfly conformation to this one is:

☐ identical ☐ enantiomeric ☐ diastereomeric

(ii) this molecule is: ☐ chiral ☐ achiral

(iii) this stereoisomer is one of how many total stereoisomers represented by this connectivity? ☐

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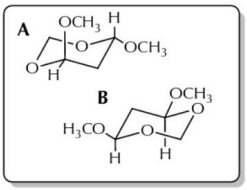
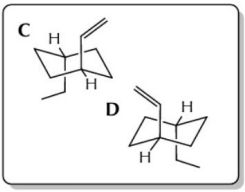
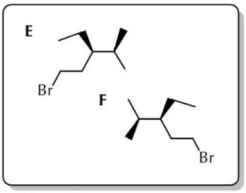
EQ 02.24

A. Consider the pairs of drawings below. Analyze each pair by checking the descriptors that apply.







(a) **A** and **B** represent
check all that apply

	the same molecule
	different molecules
	enantiomers
	constitutional (structural) isomers
	conformers of the same molecule
	A is chiral
	B is chiral

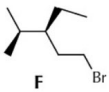
(b) **C** and **D** represent
check all that apply

	the same molecule
	different molecules
	enantiomers
	constitutional (structural) isomers
	conformers of the same molecule
	C is chiral
	D is chiral

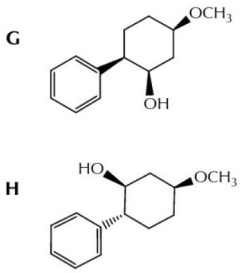
(c) **E** and **F** represent
check all that apply

	the same molecule
	different molecules
	enantiomers
	constitutional (structural) isomers
	conformers of the same molecule
	E is chiral
	F is chiral

(d) Provide the complete IUPAC name, including stereochemistry, for compound **F**.



B. An intramolecular hydrogen bond plays a role in stabilizing the most favored conformation in both of the following molecules (**G** and **H**). Both **G** and **H** have a most stable chair conformation, and if you compare the two of these most stable forms, one of them is more stable than the other. Decide which of these molecules has the most stable chair form and draw it, including the intramolecular hydrogen bond mentioned at the outset.



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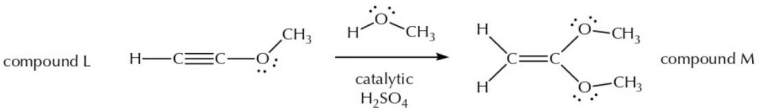
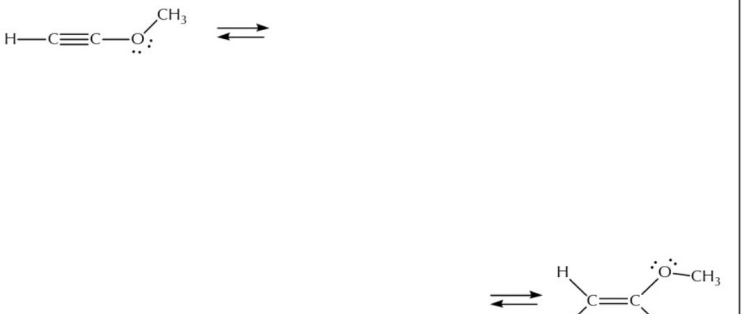
EQ 02.25

The electrophilic addition reaction of 1-methoxyethyne (compound L) with methanol (CH_3OH) in the presence of catalytic sulfuric acid gives 1,1-dimethoxyethene (compound M).



(a) Mechanistically, the acid catalyst that is present is not sulfuric acid. What is the structure of the acid that is present in solution when a small amount of sulfuric acid is added to methanol.

(b) In the space below, provide the complete, stepwise mechanism for the transformation of compound L to compound M. To keep this simple, use "H-B" for any Brønsted acid you need, and $B^{\ominus}$ for any Brønsted base.



(c) Compound M is the product associated with an addition reaction that follows the Markovnikov regioselectivity. The other orientation for the addition reaction (called the "anti-Markovnikov" orientation) actually gives a pair of $C_4H_8O_2$ diastereomers (compounds N and O). What are the structures of these two anti-Markovnikov diastereomers (note that some experimental data are given about each one of them).

compound N
(i) $C_4H_8O_2$
(ii) ^{1}H-NMR:
2 signals
(3:1 ratio)
(iii) ^{13}C-NMR:
2 signals
(iv) dipole moment:
zero

compound O
(i) $C_4H_8O_2$
(ii) ^{1}H-NR:
2 signals
(3:1 ratio)
(iii) ^{13}C-NMR:
2 signals
(iv) dipole moment:
nonzero

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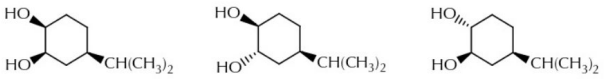
EQ 02.26

A. The following molecules were studied as a part of a new method for carrying out reactions on equatorial hydroxyl "OH" groups (*J Am Chem Soc*, **2011**, *133*, 3724). Answer the following with respect to the chair conformation that places the isopropyl "$(CH_3)_2CH$" group in an equatorial position.



compound W compound X compound Y

(a) Which of these molecules has both an axial and an equatorial hydroxyl "OH" group when the isopropyl group is an equatorial position?

circle one: W X Y

(b) In the space to the right, support your selection by drawing the chair conformation of the molecule you have selected in part (a) that has the isopropyl group in an equatorial position.

NOTE: You should also include the 3 hydrogen atoms on the ring where the isopropyl group and 2 hydroxyl groups are located. You should not include the other ring hydrogens. Be sure the direction of your axial and equatorial groups is drawn clearly.

The drawing needs to match your selection in part (a).

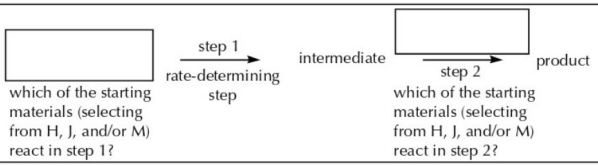
(c) In which of these molecules is an intramolecular hydrogen bond going to be impossible when conformation has the isopropyl group in the equatorial position?

circle all that apply: W X Y

B. When compounds H, J, and M are combined, a reaction takes place. The following data are known:

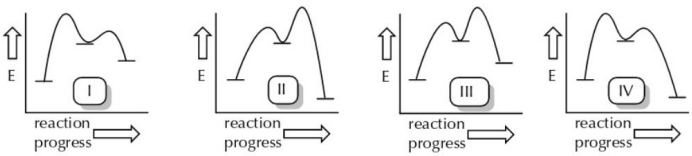
(i) the reaction occurs in two mechanistic steps, and the overall K_{EQ} is 10^5.
(ii) the first step is the rate-determining step
(iii) when the concentration of H is doubled, the reaction rate doubles
(iv) when the concentration of J is doubled, the reaction rate does not change
(v) when the concentration of M is doubled, the reaction rate doubles

(a) Complete this statement about the reaction:


step 1
rate-determining step
intermediate
step 2
product
which of the starting materials (selecting from H, J, and/or M) react in step 1?
which of the starting materials (selecting from H, J, and/or M) react in step 2?

(b) Which of these energy diagrams best describes this reaction?

circle one: I II III IV



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EQ 02.25

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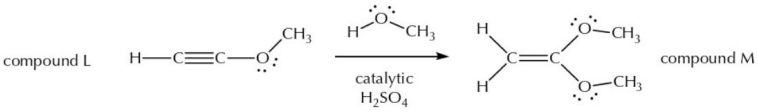
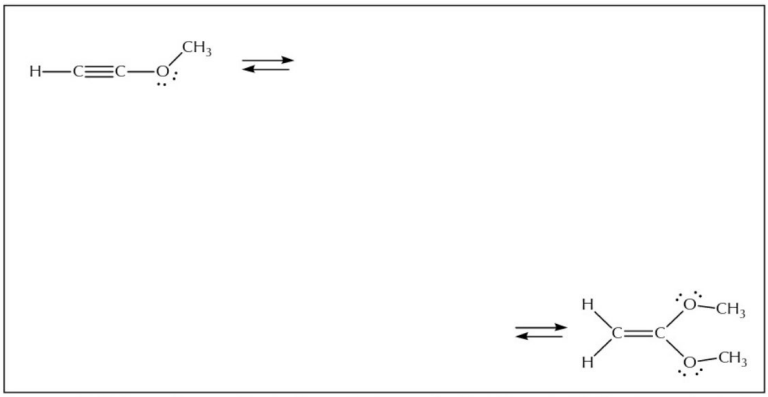


(a) Mechanistically, the acid catalyst that is present is not sulfuric acid. What is the structure of the acid that is present in solution when a small amount of sulfuric acid is added to methanol.

(b) In the space below, provide the complete, stepwise mechanism for the transformation of compound L to compound M. To keep this simple, use "H-B" for any Brønsted acid you need, and $B^{\ominus}$ for any Brønsted base.



(c) Compound M is the product associated with an addition reaction that follows the Markovnikov regioselectivity. The other orientation for the addition reaction (called the "anti-Markovnikov" orientation) actually gives a pair of $C_4H_8O_2$ diastereomers (compounds N and O). What are the structures of these two anti-Markovnikov diastereomers (note that some experimental data are given about each one of them).

compound N
(i) $C_4H_8O_2$
(ii) ^{1}H-NMR: 2 signals (3:1 ratio)
(iii) ^{13}C-NMR: 2 signals
(iv) dipole moment: zero

compound O
(i) $C_4H_8O_2$
(ii) ^{1}H-NR: 2 signals (3:1 ratio)
(iii) ^{13}C-NMR: 2 signals
(iv) dipole moment: nonzero

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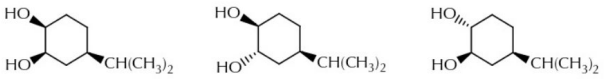
EQ 02.26

A. The following molecules were studied as a part of a new method for carrying out reactions on equatorial hydroxyl "OH" groups (*J Am Chem Soc*, **2011**, *133*, 3724). Answer the following with respect to the chair conformation that places the isopropyl "$(CH_3)_2CH$" group in an equatorial position.



compound W compound X compound Y

(a) Which of these molecules has both an axial and an equatorial hydroxyl "OH" group when the isopropyl group is an equatorial position?

circle one: W X Y

(b) In the space to the right, support your selection by drawing the chair conformation of the molecule you have selected in part (a) that has the isopropyl group in an equatorial position.

NOTE: You should also include the 3 hydrogen atoms on the ring where the isopropyl group and 2 hydroxyl groups are located. You should not include the other ring hydrogens. Be sure the direction of your axial and equatorial groups is drawn clearly.

The drawing needs to match your selection in part (a).

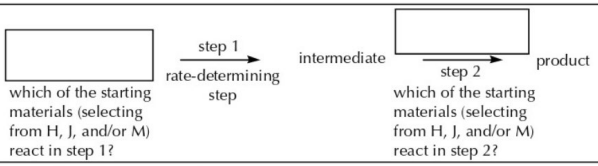
(c) In which of these molecules is an intramolecular hydrogen bond going to be impossible when conformation has the isopropyl group in the equatorial position?

circle all that apply: W X Y

B. When compounds H, J, and M are combined, a reaction takes place. The following data are known:

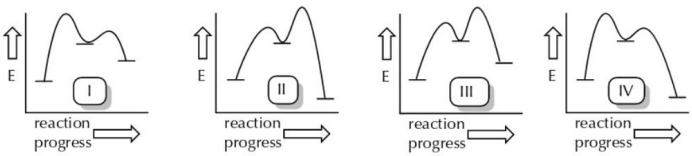
(i) the reaction occurs in two mechanistic steps, and the overall K_{EQ} is 10^5.
(ii) the first step is the rate-determining step
(iii) when the concentration of H is doubled, the reaction rate doubles
(iv) when the concentration of J is doubled, the reaction rate does not change
(v) when the concentration of M is doubled, the reaction rate doubles

(a) Complete this statement about the reaction:


step 1
rate-determining step
intermediate
step 2
product
which of the starting materials (selecting from H, J, and/or M) react in step 1?
which of the starting materials (selecting from H, J, and/or M) react in step 2?

(b) Which of these energy diagrams best describes this reaction?

circle one: I II III IV



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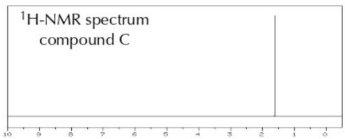
EQ 02.27

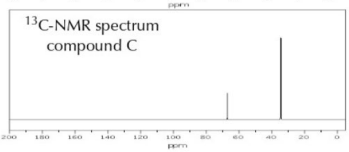
A. The following reactions result in unusual products whose identities are best determined by the spectroscopic information provided here instead of trying to predict the outcomes. Deduce the structures of these products from the information provided.

(a)

$CH_3CH_2CH_2CH_2Cl \xrightarrow[\text{toluene}]{AlCl_3,\ \text{heat}}$ compound C C_4H_9Cl

compound C



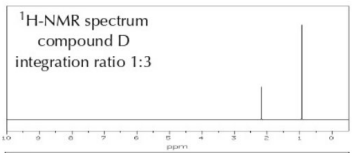


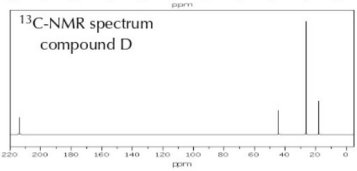
(b)

$H{-}C{\equiv}C{-}C(CH_3)_3 \xrightarrow[HgSO_4,\ HCl]{H_2O}$ compound D $C_6H_{12}O$

compound D

6

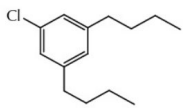




B. Draw the following compound.

(*R*)-4-methylpentane-1,2-diol

C. Name the following compound.



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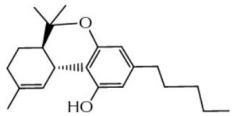
EQ 02.28

THC is the most famous of the phytocannabinoids found in cannabis plants, but cannabidiols (CBD) are similar to THC and are used more widely for therapeutic reasons when treating anxiety, chronic pain, and even inflammation. Analyze the THC and CBD below.

(a) Circle and label all sources of stereoisomerism.

THC



i. How many optically active diastereomers does this compound have?

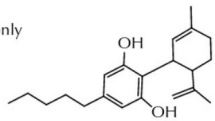
ii. Is this compound optically active?

iii. Estimate the pK_a for the most acidic proton on THC.

(b) Circle all sources of stereoisomerism.

CBD

connectivity only

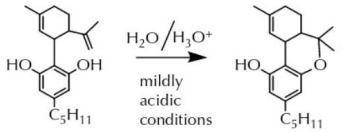


i. How many molecules in total does this drawing represent?

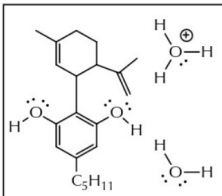
ii. How many molecules represented by this connectivity are optically active?

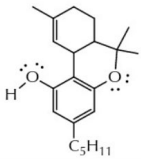
iii. How many atoms in CBD are sp^2 hybridized?

(c) Under aqueous conditions, CBD reacts in a way that is analagous to the catalyzed addition reactions you have seen, forming THC. This 3-step transformation can be shown using (in the first step) and regenerating (in the last step) the real acid. Ignoring stereochemistry, show the complete stepwise mechanism for this intramolecular (within the same molecule) addition reaction of a weak acid group.



CBD **THC**





(d) One of the rings in CBD provides an interesting starting material for electrophilic addition. Draw the completely regioselective product (connectivity only) and address the stereochemistry questions about how many molecules are represented by the starting material and the product.

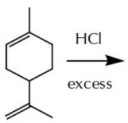
i. The "CBD ring" (at right) represents (*circle one*):

a pair of enantiomers

a pair of diastereomers

3 stereoisomeric molecules

4 stereoisomeric molecules



CBD ring

HCl

excess

ii. product

iii. This product forms as (*circle one*):

a pair of enantiomers

a pair of diastereomers

3 stereoisomeric molecules

4 stereoisomeric molecules

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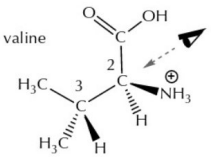
EQ 02.29

Valine is an essential amino acid that has been studied for years because of its unique role in a variety of protein functions (e.g. sickle cell anemia) and metabolic disorders. Most recently, researchers are looking at its potential role (and the role of its catabolites) in the treatment of diabetes because a valine-depleted diet may lead to increased insulin sensitivity.

A. Using Newman projections, draw, for the C2–C3 bond:
(a) the conformation shown here
(b) the least stable staggered conformation
(c) the least stable conformation, overall

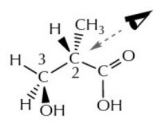
Be sure to view the bond down the 2–3 bond as indicated.



The conformation as shown above	Least stable staggered conformation	Least stable conformation overall
(a)	(b)	(c)

B. Compound 1 is a metabolic breakdown product of valine. The carbon-carbon bond highlighted (C2–C3) is shown in its most stable conformation, accounting for over 99% of the equilibrium population. Using a Newman projection (view with carbon 2 in front), show this conformation and indicate two reasons for its stability. Note: you must describe the structural features in this compound specifically.

compound 1



most stable staggered conformation

(a) Most stable staggered conformation

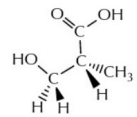
(b) Two stabilizing factors - be very clear and specific

1)

2)

(c) Answer the following about compounds 1 and 2

compound 2



There are (mark all that are true):

- ☐ different molecules
- ☐ constitutional isomers
- ☐ stereoisomers
- ☐ enantiomeric conformations of the same molecule
- ☐ diastereomeric conformations of the same molecule
- ☐ both optically active
- ☐ both shown in their most stable conformation
- ☐ diastereomers
- ☐ enantiomers

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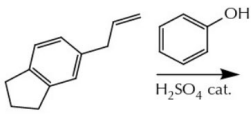
EQ 02.30

Complete the following addition reactions by providing the requested information. When you are asked to draw all products, be sure to show clearly the connectivity and stereochemistry that makes each product unique. If regioselectivity is indicated, only major regioisomer(s) are expected to form.

A. This first reaction is highly regioselective, and yields two products.

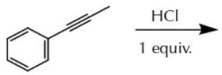


(a) Draw the two organic products.

(b) These two products are *(check all that apply)*:

- ☐ enantiomers
- ☐ diastereomers
- ☐ constitutional isomers

B. This second reaction is highly regioselective, and yields two products.



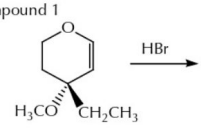
(a) Draw the two organic products (both are C_9H_9Cl).

(b) These two products are *(check all that apply)*:

- ☐ enantiomers
- ☐ diastereomers
- ☐ constitutional isomers

C. Compounds 1 and 2, shown below, are $C_8H_{14}O_2$ structural isomers. Draw one of the products that form when these compounds undergo addition. Draw it carefully, showing connectivity and stereochemistry as necessary. Then predict how many other products will form. If high regioselectivity is predicted to occur, you may assume only the major regioisomer will form.

compound 1

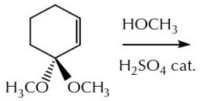


(a) Draw one product

(b) This product will form with *(check all that apply)*:

- ☐ no other isomer(s)
- ☐ its enantiomer
- ☐ its diastereomer(s)
- ☐ regioisomer(s)

compound 2



(c) Draw one product

(d) This product will form with *(check all that apply)*:

- ☐ no other isomer(s)
- ☐ its enantiomer
- ☐ its diastereomer(s)
- ☐ regioisomer(s)

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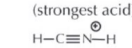
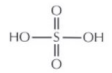
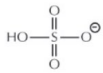
ACID	pK_a	CONJUGATE BASE
(strongest acid)		(weakest base)
	-12	
	-9	
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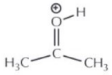	-7.2	
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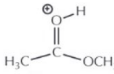	-4.6	
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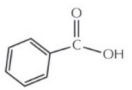
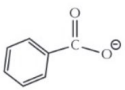
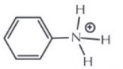
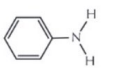
	4.2	
	4.6	
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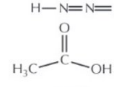
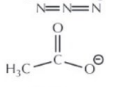
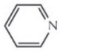
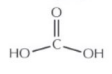
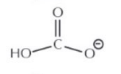
	4.8	
	5.2	
	6.5	
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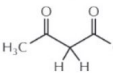
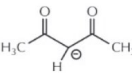
	9.2	

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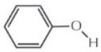
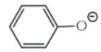
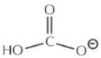
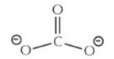
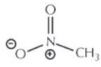
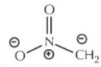
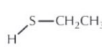
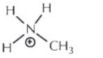
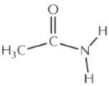
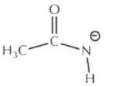
	10.0	
	10.2	
	10.2	
	10.5	
	10.6	
	15.0	
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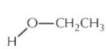
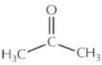
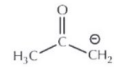
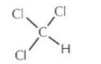
	17	
	19	
	25	
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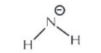
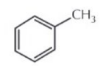
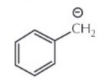
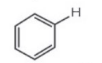
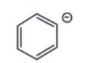
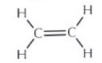
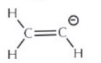
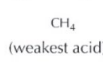
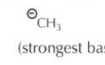
	36	
	41	
	43	
	44	
 (weakest acid)	49	 (strongest base)

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PERIODIC TABLE OF THE ELEMENTS

GROUP

PERIOD	1 IA	2 IIA	3 IIIB	4 IVB	5 VB	6 VIB	7 VIIB	8 VIIIB	9 VIIIB	10 VIIIB	11 IB	12 IIB	13 IIIA	14 IVA	15 VA	16 VIA	17 VIIA	18 VIIIA
1	1 H Hydrogen 1.008																	2 He Helium 4.00
2	3 Li Lithium 6.94	4 Be Beryllium 9.01											5 B Boron 10.81	6 C Carbon 12.01	7 N Nitrogen 14.01	8 O Oxygen 16.00	9 F Fluorine 19.00	10 Ne Neon 20.18
3	11 Na Sodium 22.99	12 Mg Magnesium 24.31											13 Al Aluminum 26.98	14 Si Silicon 28.09	15 P Phosphorus 30.97	16 S Sulfur 32.06	17 Cl Chlorine 35.45	18 Ar Argon 39.95
4	19 K Potassium 39.10	20 Ca Calcium 40.08	21 Sc Scandium 44.96	22 Ti Titanium 47.87	23 V Vanadium 50.94	24 Cr Chromium 52.00	25 Mn Manganese 54.94	26 Fe Iron 55.85	27 Co Cobalt 58.93	28 Ni Nickel 58.69	29 Cu Copper 63.55	30 Zn Zinc 65.38	31 Ga Gallium 69.72	32 Ge Germanium 72.63	33 As Arsenic 74.92	34 Se Selenium 78.97	35 Br Bromine 79.90	36 Kr Krypton 83.80
5	37 Rb Rubidium 85.47	38 Sr Strontium 87.62	39 Y Yttrium 88.91	40 Zr Zirconium 91.22	41 Nb Niobium 92.91	42 Mo Molybdenum 95.95	43 Tc Technetium	44 Ru Ruthenium 101.07	45 Rh Rhodium 102.91	46 Pd Palladium 106.42	47 Ag Silver 107.87	48 Cd Cadmium 112.41	49 In Indium 114.82	50 Sn Tin 118.71	51 Sb Antimony 121.76	52 Te Tellurium 127.60	53 I Iodine 126.90	54 Xe Xenon 131.29
6	55 Cs Cesium 132.91	56 Ba Barium 137.33	57–71	72 Hf Hafnium 178.49	73 Ta Tantalum 180.95	74 W Tungsten 183.84	75 Re Rhenium 186.21	76 Os Osmium 190.23	77 Ir Iridium 192.22	78 Pt Platinum 195.08	79 Au Gold 196.97	80 Hg Mercury 200.59	81 Tl Thallium 204.38	82 Pb Lead 207.2	83 Bi Bismuth 208.98	84 Po Polonium	85 At Astatine	86 Rn Radon
7	87 Fr Francium	88 Ra Radium	89–103	104 Rf Rutherfordium	105 Db Dubnium	106 Sg Seaborgium	107 Bh Bohrium	108 Hs Hassium	109 Mt Meitnerium	110 Ds Darmstadtium	111 Rg Roentgenium	112 Cn Copernicium	113 Nh Nihonium	114 Fl Flerovium	115 Mc Moscovium	116 Lv Livermorium	117 Ts Tennessine	118 Og Oganesson

ALKALI METALS · ALKALINE EARTH METALS · TRANSITION METALS · P-BLOCK METALS · METALLOIDS · NON-METALS · HALOGENS · NOBLE GASES

Key:
11 — Atomic number
Na — Element symbol
Sodium — Element name
22.99 — Standard atomic weight (No data given for elements without stable nuclides.)

State at standard temperature and pressure (0 °C and 1 atm):
Solid
Liquid
Gas
Unknown

LANTHANOIDS	57 La Lanthanum 138.91	58 Ce Cerium 140.12	59 Pr Praseodymium 140.91	60 Nd Neodymium 144.24	61 Pm Promethium	62 Sm Samarium 150.36	63 Eu Europium 151.96	64 Gd Gadolinium 157.25	65 Tb Terbium 158.93	66 Dy Dysprosium 162.50	67 Ho Holmium 164.93	68 Er Erbium 167.26	69 Tm Thulium 168.93	70 Yb Ytterbium 173.05	71 Lu Lutetium 174.97
ACTINOIDS	89 Ac Actinium	90 Th Thorium 232.04	91 Pa Protactinium 231.04	92 U Uranium 238.03	93 Np Neptunium	94 Pu Plutonium	95 Am Americium	96 Cm Curium	97 Bk Berkelium	98 Cf Californium	99 Es Einsteinium	100 Fm Fermium	101 Md Mendelevium	102 No Nobelium	103 Lr Lawrencium

RARE EARTH METALS

Notes: "Caesium" and "aluminium" are the internationally recognized spellings for "cesium" and "aluminum." An atomic weight (relative atomic mass) of an element from a specified source is the ratio of the average mass per atom of the element to 1/12 of the mass of an atom of ^{12}C (IUPAC). Sources: IUPAC periodic table 28 November 2016; *Pure and Applied Chemistry* **88**, No. 3 (2016).

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